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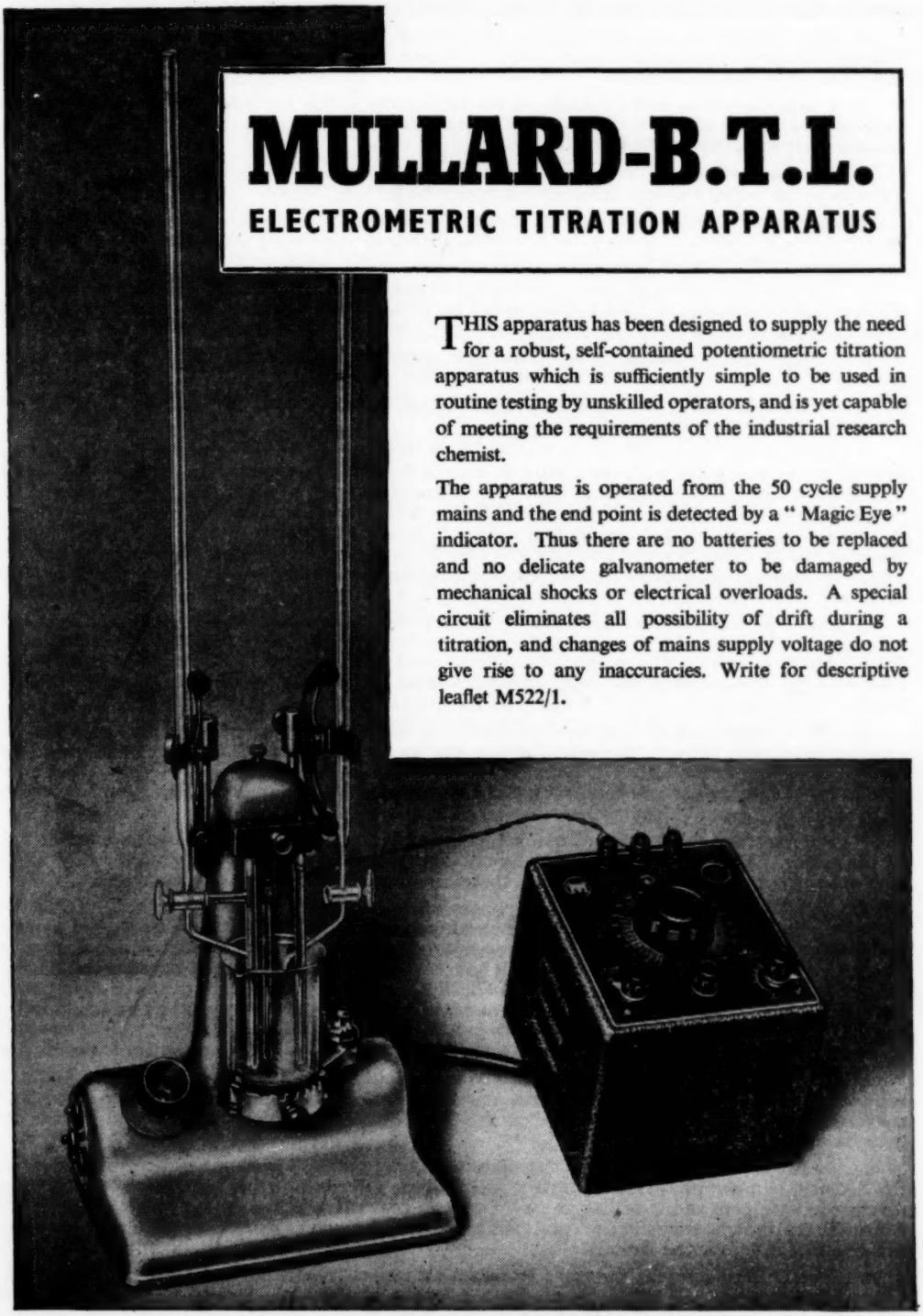

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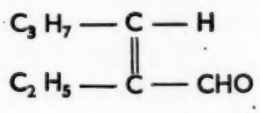

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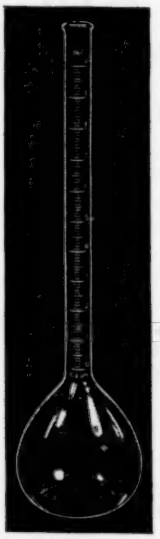

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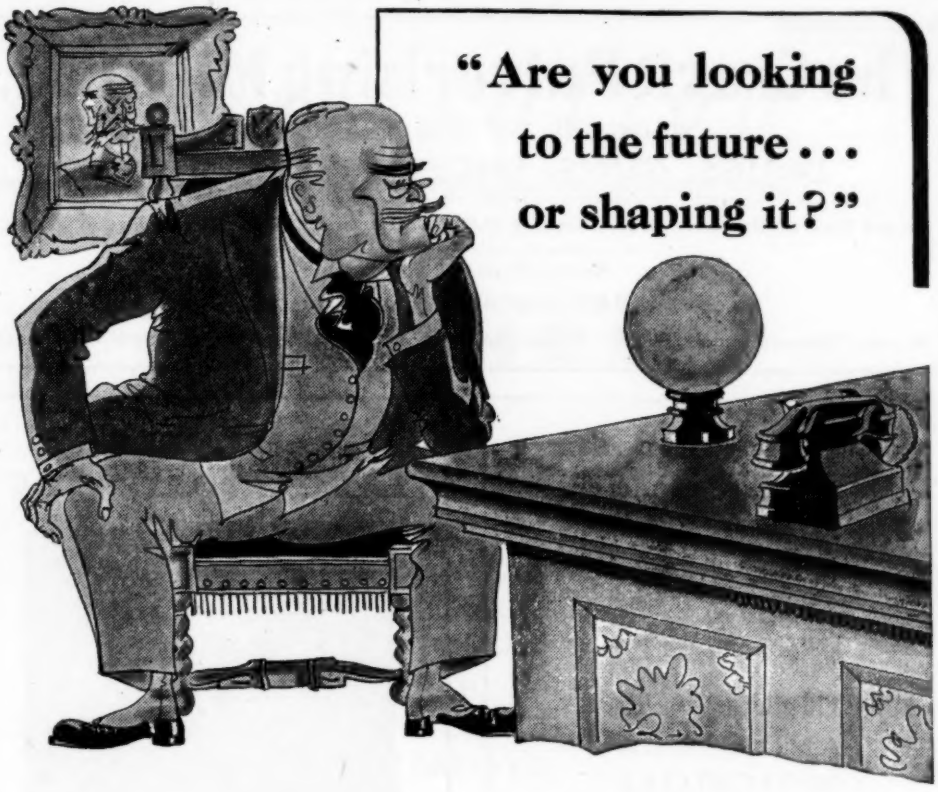

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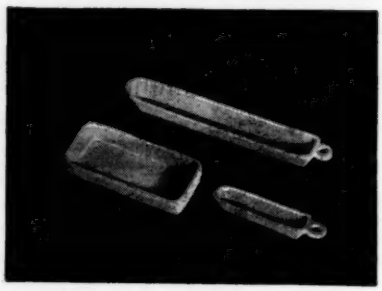

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206 *In the scheme, left hand side, second m.p. from bottom, for* " 56—57° " *read* " 55—56° "; *right hand side, second m.p. from bottom, for* " 55—56° " *read* " 56—57° ".

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163 *In the Table, the heading* " Series A . . ." *should precede the line above it.*
164 *On the Figure, for the numerals* " 100, 80, 60, 40, 20 " *on the lower half of the ordinate, read respectively* " 0, 20, 40, 60, 80 ".

amino group greatly activated the pyridine nucleus. The phenomena of tautomerism in the amino-pyridines and -picolines observed and studied by Tchitchibabine and his collaborators also increased the theoretical interest and the variety of possible applications of this work. Again, by studying the action of alkyl halides on sodium derivatives of picoline, Tchitchibabine succeeded in obtaining higher homologues of pyridine.

His fundamental work on pyridine chemistry, a subject which has been gaining in importance ever since, led to the synthesis of a great variety of natural products, pharmaceutical chemicals, etc. Tchitchibabine's research was not, however, confined to this field; he did outstanding work in other branches of chemistry. At the beginning of the century he carried out extensive research on the problem of tervalent carbon, and in 1912 he was invited to England by the British Association to lecture on this subject. There were, too, his investigations of the composition and synthesis of various alkaloids and other plant products (pilocarpine, santonin, bergenin, etc.), his work on the alkylation of phenols in the presence of various condensing agents, in particular phosphoric acid, his study of new reactions with organomagnesium compounds which led to methods of synthesis of acetals and alkoxy-ethylenic acids, and his study of naphthenic acids from Russian oils. We also owe to him the synthesis of thiodiglycol from ethylene oxide and hydrogen sulphide.

In 1924 appeared in Russia his treatise " Basic Principles of Organic Chemistry " which has been revised several times and also translated into French. As we open the book we read : " To the memory of Natacha Tchitchibabine, my beloved daughter, my ablest assistant and my best friend, I dedicate my life's work." Natacha, his only child, also a chemist, was killed in 1930 in an explosion in a chemical products factory.

Tchitchibabine was fortunate in having by his side, throughout his brilliant but arduous career, his wife Vera Vladmirovna Tchitchibabine, also a scientist, whom he had known from her schooldays.

I. MARSZAK.

KAPILRAM HARDEVRAM VAKIL.

1884—1946.

MR. KAPILRAM HARDEVRAM VAKIL was born in Surat (India) on 28th May, 1884, of a family of lawyers, and was a grandson of the late Mr. Nanabhai Haridas, the first Indian Judge of the Bombay High Court. He was educated at Bharda New High School, Bombay, Elphinstone College, Bombay, and Manchester College of Technology. He passed the B.A. examination of the University of Bombay in 1906, and was awarded the Bell Prize in Physics. He proceeded to England in 1909 for further studies and obtained the B.Sc. (Tech.) degree of the University of Manchester with First Class Honours in dyeing, bleaching, and oils and fats. On his return to India he joined the Jamshed Oil Mills of Tatas at Kurla as manager and consulting chemist and did the pioneering work of developing the cotton-seed oil industry in India. Later, he started independent consultant practice and helped a number of industrial concerns with his technical advice.

He was greatly interested in research work from the beginning of his career, and his first paper, on the chemical examination of ghee, was published in 1915 (*J. Soc. Chem. Ind.*, **34**, 320). He had invented and was the patentee of several processes for refining oils and fats. During the First World War he proceeded in 1916 to the Manchester College of Technology and was awarded the Manchester Corporation special research scholarship. During this period he carried out, in collaboration with Prof. Green, research work on the sulphonation of β-naphthylamine which was published in the *Journal* (1918, **113**, 35). While he was in England he read an important and valuable paper on cotton-seed products before the Manchester Branch of the Society of Chemical Industry which was subsequently published (*J. Soc. Chem. Ind.*, 1917, **36**, 685). He was awarded the M.Sc. (Tech.) degree of the University of Manchester in 1917 and was also admitted to the Associateship of the Institute of Chemistry, of which he became a Fellow later. He received an offer of the Privy Council Scholarship for continuing research work at Manchester and was invited by Lever Bros. to act as their consultant in the East, but he preferred to join the Tatas as consulting chemist and in this capacity he carried out surveys and research work on a number of important industrial problems.

Early in his career, Vakil had realised the great importance of establishing key chemical industries—particularly the alkali industry—in India, and his whole life was devoted towards the achievement of this ideal. As early as 1917, he carried out extensive surveys for a suitable site for salt works on the Eastern coast of India for the then proposed heavy chemicals, etc., industries of Tatas at Sakchi (now Jamshedpur), and in 1920 he investigated the prospects of establishing an alkali industry at Kodinar in Kathiawar. In this connection he was also deputed by Tatas in 1920—1921 to visit the various alkali works in Europe and America, and had discussions and consultations with a number of well-known alkali experts. In 1923 his services were engaged by Dhrangadhra State (Kathiawar) for their soda-ash project which he successfully completed, and in 1926 he started the Okha Salt Works at Mithapur, where he carried out his pioneering work of recovering and manufacturing important by-products from bitterns. In 1937 the Tatas accepted his scheme for establishing the heavy chemicals industry at Mithapur (Kathiawar), and Tata Chemicals, Limited, was finally started in 1939 with Vakil as Technical Director. Tata Chemicals is the largest chemical concern in India and is the crowning glory and fulfilment of his life's mission.

Vakil was a member of a number of scientific societies, and had the distinction of being the first Indian to be elected directly to the full membership of the Institute of Chemical Engineers and also to the membership of the Society of Public Analysts. He contributed a number of original papers to scientific journals and is the

author of two authoritative books on salt and Indian coal. His advice was sought by a number of organisations and he served on a large number of important Government and other Committees. He was held in the highest esteem by his friends, colleagues, and subordinates, and the Government of Baroda bestowed on him the high honour of Raj Ratna in recognition of his services in developing the salt industry in the State.

Vakil was a very widely travelled man and had visited foreign countries a number of times. In his early days he was an active member of Indian National Congress, but on the advice of Mahatma Gandhi left politics and devoted his whole attention to the development of chemical industries in India. To attain his long cherished goal of putting India on the industrial map of the world he spared no pains and lived the life of a recluse wholly devoted to work. As a result of long and continuous hard work his health broke down last year and he was advised to rest. He, however, was so devoted to work that he disregarded the advice of his physicians and died in harness on 29th January, 1946, through heart failure. His death has been a great loss not only to his family and friends, but also to India, who has lost by his death one of her ablest and most eminent technical chemists and chemical engineers.

N. A. YAJNIK.

ERNEST ADAM WAGSTAFF.

1907—1942.

PILOT OFFICER ERNEST ADAM WAGSTAFF was shot down over France on October 25th, 1942, and lies, with his air-crew, buried at Moulin-sur-Touvent some 25 miles N.E. of Paris.

He was educated at Nottingham High School and the University College of Nottingham. As an undergraduate, although his physical presence was conspicuous his reticence and diffidence made him little known. As a research student it was otherwise. After a short spell in a sugar beet factory he returned to the college to engage in research in organic chemistry. A little the senior of the other students and a lot taller he assumed a station *in loco parentis*, his former diffidence vanished and his strikingly original character revealed itself. He studied the nitration of β-phenylethyl-, styryl-, and phenylacetylenyl-pyridines and, as one of his contemporaries remarked, " he nitrated stilbazole with a zeal which was at once an example to, and the wonder of, us all." The results of the work were published in four papers in the *Journal*.

Wagstaff's enthusiasm for organic chemistry was not born of a narrow-minded lack of interest in all else. He was well acquainted with all branches of chemistry and had not a little knowledge of botany and geology. Outside science his interests ranged from mediaeval alabaster carvings and windmills to Norman castles in Pembroke and Iron-Age camps in Dorset, from the operettas of Gilbert and Sullivan to the writings of Belloc, Chesterton, and A. E. Housman. He was an excellent shot with both the ·22 and the service rifle, and was a member of the winning Nottingham Team in the Inter-Universities Small-Bore Championship. He walked extensively both in this country and on the continent and attended the Sixth International Congress of Agricultural Chemists at Budapest in 1939.

As a writer of letters he was inimitable and could express himself as readily in verse as in prose; in choice of word and turn of phrase he was always original and often strikingly effective.

After obtaining the degree of Ph.D. of London University Wagstaff joined the Research Department of the Distillers Company in January 1933. From 1934 to 1937 he was in charge of the Molasses Control Laboratory. From April 1937 until he joined the Royal Air Force as a volunteer he was one of a team of workers engaged in process development work in connection with a vapour-phase catalytic oxidation reaction.

It may have been the repeated bombing to which he was subjected whilst engaged in the erection of a chemical plant that induced him, in October 1940, to enlist in the Royal Air Force. He did not analyse his motives to others but said later that he did not regret his decision except insofar as his action made others restless. Writing from " the quiet of an R.A.F. training camp " he said that, hearing of the trials under bombing of those left behind in his former job, he felt " something of a shirker." He made friends in the R.A.F. and seemed to enjoy barrack life for its own sake. After training in this country and in North America he was commissioned in April 1942, and saw much of the Britain he loved before those inimitable letters, coming now from an aerodrome in Lincolnshire, suddenly ceased.

Wagstaff's original work was, for the most part, not for publication; this circumstance, together with his untimely death, prevented him from making for himself a name in chemistry commensurate with his talents. He died, as he had lived, for an ideal; in the lives of the few who knew him well his passing leaves a void which can never be filled.

B. D. SHAW.

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156. *Amidines. Part II. Preparation of Cyanides, Amides, and Amidines from Carboxylic Acids.*

By P. Oxley, M. W. Partridge, T. D. Robson, and W. F. Short.

Evidence is advanced to show that five intermediate stages may be distinguished in the production of amidine sulphonates from carboxylic acids and sulphonamides. The conditions of the reaction can be modified so that cyanides and, in some cases, amides may be obtained in good yield.

Hartman (Diss., Johns Hopkins Univ., 1894; Remsen, Hartman, and Muckenfuss, *Amer. Chem. J.*, 1896, **18**, 150) showed that *p*-sulphonamidobenzoic acid afforded a monoammonium salt of *p*-sulphobenzoic acid when heated at its melting point, whereas at a higher temperature phenyl cyanide was obtained. Muckenfuss (*ibid.*, p. 349) found that if the acid is kept at 220° for a considerable time one of the products (" infusible diamide ") is a stable, neutral compound isomeric with *p*-sulphonamidobenzamide. Nakaseko (1899) suggested that this compound is benzamidine-*p*-sulphonic acid, and this was confirmed by Rouiller (*ibid.*, 1912, **47**, 475), who showed that a number of carboxylic acids were converted into amidine benzenesulphonates when heated in sealed tubes at 225° for 5 hours with benzenesulphonamide (2 mols.). Rouiller concluded that the reaction may be represented by the equation

$$R\cdot CO_2H + 2Ph\cdot SO_2\cdot NH_2 \longrightarrow R\cdot C(:NH)\cdot NH_2,Ph\cdot SO_3H + Ph\cdot SO_3H$$

which in the case of benzoic acid was expanded to

$$Ph\cdot CO_2H + Ph\cdot SO_2\cdot NH_2 \longrightarrow Ph\cdot CO\cdot NH_2 + Ph\cdot SO_3H$$
$$Ph\cdot CO\cdot NH_2 + Ph\cdot SO_2\cdot NH_2 \longrightarrow Ph\cdot C(:NH)\cdot NH_2,Ph\cdot SO_3H$$

although it was shown that benzamide and benzenesulphonamide did not in fact yield benzamidine benzenesulphonate at 220° unless free benzenesulphonic acid (1 mol.) was also present. He also observed that phenyl cyanide (19·4%) is produced as a by-product in the reaction between benzoic acid and benzenesulphonamide at 225°, and at higher temperatures (300°) sufficient is produced to form a layer above the solidified reaction product. Amidines were also obtained from acetic acid, *m*-nitrobenzoic acid (15·5%), *p*-nitrobenzoic acid (31%, and 27% of cyanide), *m*-bromobenzoic acid (18·3%), phenylacetic acid (42·6%), and terephthalic acid, which also gave *p*-phenylene dicyanide (48%) and *p*-cyanobenzoic acid (3·4%). Phthalic acid gave a quantitative yield of phthalimide, and *iso*phthalic acid afforded the corresponding dicyanide (46·7%) and *m*-cyanobenzoic acid (6·8%). Neither amidines nor cyanides were obtained from chloroacetic, oxalic, malonic, tartaric, salicylic, *o*-anisic, *p*-hydroxy-, *o*-nitro-, and *o*- and *p*-amino-benzoic acids.

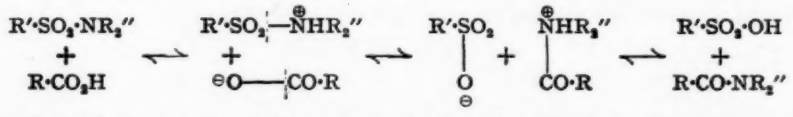
As the result of a detailed study of the reactions between carboxylic acids and sulphonamides we suggest that the production of amidine sulphonates may be represented as follows

$$R\cdot CO_2H + R'\cdot SO_2\cdot NH_2 \longleftrightarrow R\cdot CO\cdot NH_2 + R'\cdot SO_2\cdot OH \quad (I)$$
$$R\cdot CO\cdot NH_2 + R'\cdot SO_2\cdot NH_2 + R'\cdot SO_2\cdot OH \longrightarrow R\cdot CO\cdot NH\cdot SO_2R' + R'\cdot SO_2\cdot ONH_4 \quad (II)$$
$$R\cdot CO\cdot NH\cdot SO_2R' \longleftrightarrow R\cdot C(:NH)\cdot O\cdot SO_2R' \quad (III)$$
$$R\cdot C(:NH)\cdot O\cdot SO_2R' \longrightarrow R\cdot CN + R'\cdot SO_2\cdot OH \quad (IV)$$
$$R\cdot CN + R'\cdot SO_2\cdot ONH_4 \longleftrightarrow R\cdot C(:NH)\cdot NH_2,R'\cdot SO_2\cdot OH \quad (V)$$

The evidence for the five stages postulated will be discussed in turn. Indirect evidence for the exchange of functions between the carboxylic acid and the sulphonamide is provided by the observation that benzoic acid and benzenesulphondimethylamide (1 mol.) react exothermically at 230° to yield benzdimethylamide (83%) and benzenesulphonic acid. Similarly, nicotinodiethylamide (nikethamide) is obtained in 81% yield by heating *nicotinic acid benzenesulphonate* and benzenesulphondiethylamide at 220°.* In these examples the reaction cannot proceed beyond Stage I, and more direct evidence for the functional exchange is provided by the observation that the reaction between a carboxylic acid and an unsubstituted sulphonamide can be arrested at this stage. If the reaction between a carbonamide and a sulphonamide is correctly represented by (II), the sulphonic acid (or its anion) acting as an indispensable neutralising agent, then it should be possible to arrest the reaction at Stage I by arranging the experimental conditions so that the acid produced at this stage is neutralised immediately. In agreement with this deduction, *nicotinamide benzenesulphonate* is produced when nicotinic acid and benzenesulphonamide (2 mols.) are heated at 225°. On the other hand, nicotinic acid benzenesulphonate and benzenesulphonamide (2·4 mols.) afford *3-cyanopyridine benzenesulphonate* (75%) when heated at 230° for 40 minutes. When the carboxylic acid contains no basic group the reaction may be arrested at Stage I by mean of an added base. Thus, *p*-carboxyphenyl methyl sulphone, benzenesulphonamide (1·02 mols.), and pyridine (1·0 mol.) afford *p*-carbamylphenyl methyl sulphone, $Me\cdot SO_2\cdot C_6H_4\cdot CO\cdot NH_2$, in 34% yield when heated under reflux. Pyridine and quinoline almost completely inhibit the reaction between benzoic acid and benzenesulphonamide at 230—250°, and it seems that the sulphonamide–carboxylic acid exchange is catalysed by acids; for instance, addition of a small amount of sulphonic acid reduces or eliminates the period of induction sometimes observed in the reaction between a sulphonamide and a weak carboxylic acid and shortens the duration of the first weakly exothermic phase in the reaction between benzenesulphonamide and *p*-nitrobenzoic acid

* See Boots Pure Drug Co., Oxley and Short, B.P. Appln., 1429/17.1.45.

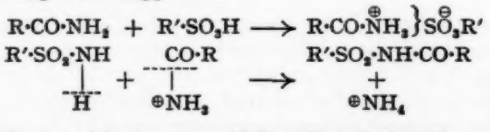
(see Fig.). It is improbable that an intermediate of the type $R{\cdot}C(OH)_2{\cdot}NH{\cdot}SO_2R'$ intervenes in the sulphonamide–acid exchange, since it should spontaneously lose water to give $R{\cdot}CO{\cdot}NH{\cdot}SO_2R'$ which is known to decompose rapidly to cyanide (III and IV) at the temperature employed for the production of carbonamides. Moreover, the liberation of steam has not been observed, and the yields of cyanides are frequently so high that very little hydrolysis could occur during the course of the reaction. The production of an addition compound would be impossible when a dialkylsulphonamide is involved and the following mechanism is suggested



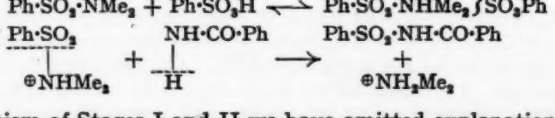
(The dotted lines indicate the fate of the electron pairs originally forming the covalent bonds which are broken.)

Fission of the kation $R'{\cdot}SO_2{\cdot}\overset{\oplus}{N}HR_2''$ is doubtless promoted by repulsion between the integral charge on the nitrogen atom and the fractional charge on the sulphur atom of the SO_2 double dipole. The stages in the interaction between the kation and the anion are regarded as simultaneous and not successive, so that the amine is never kinetically free. The catalytic effect of added sulphonic acid on the amide exchange may be due to an increase in the concentration of the kation $R'{\cdot}SO_2{\cdot}\overset{\oplus}{N}HR''_2$.

Rouiller (*loc. cit.*) found that the presence of benzenesulphonic acid (the monohydrate was used) is essential for the production of benzamidine benzenesulphonate by heating benzamide and benzenesulphonamide in a sealed tube at 220°, and we find that addition of *ca.* 0·5 mol. of benzenesulphonic acid is necessary to produce the maximum yields of phenyl cyanide and of ammonium benzenesulphonate when the reactants are heated at 235° for 20 minutes in an open vessel. The assumption that phenyl cyanide is produced by simple dehydration of benzamide, the water formed being utilised in the hydrolysis of the benzenesulphonamide under the catalytic influence of the sulphonic acid, is at variance with the stability of benzamide at 235° and the resistance of benzenesulphonamide to hydrolysis under the conditions employed in the experiment. Addition of benzenesulphonic acid (1/15 mol.) accelerates the reaction between *p*-carboxyphenyl methyl sulphone and benzenesulphonamide (2 mols.), so that the optimum yield of *p*-cyanophenyl methyl sulphone is obtained after 50 minutes at 225°, whereas in absence of the acid the reaction is incomplete in this time, the yield being 18% lower, and the deficit appears in the form of N-p-*methylsulphonylbenzoylbenzenesulphonamide*, $Me{\cdot}SO_2{\cdot}C_6H_4{\cdot}CO{\cdot}NH{\cdot}SO_2Ph$, m. p. 215°. This compound can also be obtained from benzenesulphonamide and *p*-methylsulphonylbenzoyl chloride and it seems clear that " mixed imides " of this type are the precursors of the cyanides produced from carboxylic acids and sulphonamides (II). Two exothermic phases can be distinguished in the reaction leading to the production of *p*-nitrophenyl cyanide (see Fig.), the first representing the acid–amide exchange (I), and the second the decomposition of the mixed imide (III and IV), and by interrupting the reaction before the onset of the second exothermic stage, N-p-*nitrobenzoylbenzenesulphonamide* (69%) can be isolated from the product. N-p-*Ethylsulphonyl-* and N-o-*nitro-benzoylbenzenesulphonamide* have also been isolated as products of the reaction between benzenesulphonamide and the appropriate acid. A small yield of *N*-benzoylbenzenesulphonamide can be obtained by heating an equimolecular mixture of benzamide, benzenesulphonamide, and benzenesulphonic acid at 155° (II), and the following mechanism, analogous to that involved in Stage I, is suggested



Equimolecular proportions of benzamide, benzenesulphondimethylamide, and benzenesulphonic acid react at 230—235° to give phenyl cyanide (82%) and dimethylammonium benzenesulphonate (75%), and this reaction may well proceed by the production of the mixed imide by the following mechanism



In discussing the mechanism of Stages I and II we have omitted explanations based on the production of addition compounds containing hexacovalent sulphur, since, notwithstanding the existence of sulphur hexafluoride, there is, so far as we are aware, no evidence which unequivocally demands that sulphur behaves in this way in organic compounds containing the groups ·SO· and ·SO_2·, and there is much evidence to the contrary (see also Rothstein, *J.*, 1940, 1550).

Wallach (*Annalen*, 1882, **214**, 211) showed that benzenesulphonamide and benzoyl chloride at 140—160° afford *N*-benzoylbenzenesulphonamide, m. p. 147°, whereas at higher temperature the main products are benzenesulphonic acid and cyaphenin. We find that if *N*-benzoylbenzenesulphonamide is heated at 190—195° so that the cyanide distils, an almost quantitative yield of phenyl cyanide is obtained and 82% of the calculated

amount of benzenesulphonic acid can be isolated from the residue (as guanidine salt). *N*-*p*-Methylsulphonylbenzoylbenzenesulphonamide affords a 95% yield of *p*-cyanophenyl methyl sulphone when heated at 230° for an hour. Similarly, *N*-*o*-nitrobenzoylbenzenesulphonamide gives a 41% yield of *o*-nitrophenyl cyanide on heating, the *p*-isomer affords 81% of *p*-nitrophenyl cyanide, and a 50% yield of methyl cyanide is obtained by the dry distillation of sulphacetamide (*p*-aminobenzenesulphonylacetamide). The decomposition of the mixed imide to cyanide and sulphonic acid (IV) is therefore well established, and the isomerisation postulated (III) is analogous to that which occurs in the Beckmann transformation of oximes. An alternative mechanism involving isomerisation to R·C(OH):N·SO_2·R′, followed by decomposition to R·CN and R′·SO_3H, is less acceptable, since it will be shown in a subsequent communication that the reactions of the substituted imides R·CO·NR″·SO_2·R′ are best explained by postulating isomerisation to R″N:CR·O·SO_2·R′. The fact that mixed imides cannot be obtained from an arylsulphonyl chloride and an amide is doubtless due to the production of an arylsulphonyl*iso*amide, R′·SO_2·O·CR:NH, which immediately decomposes to a cyanide and a sulphonic acid (see Wolkow, *Ber.*, 1871, **4**, 290; Meister, Lucius, and Brüning, G.P. 380,323; Gwan, *J. Indian Chem. Soc.*, 1941, **18**, 164). We find that benzamide and benzenesulphonyl chloride at 125—130° afford a 78% yield of phenyl cyanide and a small amount of *benzamide benzenesulphonate*, m. p. 121·5—122°.

Stage V, the conversion of the cyanide into the amidine sulphonate, has been discussed in detail in Part I (Oxley and Short, this vol., p. 147) in which many examples of this reaction are recorded.

We find that benzoic anhydride and *p*-nitrobenzoic anhydride react with benzenesulphonamide to give the corresponding cyanide, the optimum yields being obtained when the reactants are in the proportion required by the equation

$$(R\cdot CO)_2O + 3R'\cdot SO_2\cdot NH_2 \longrightarrow 2R\cdot CN + 2R'\cdot SO_3H + R'\cdot SO_2NH_4$$

It may be assumed that a mixed imide is also produced as an intermediate in this case

$$(R\cdot CO)_2O + R'\cdot SO_2\cdot NH_2 \longrightarrow R\cdot CO\cdot NH\cdot SO_2\cdot R' + R\cdot CO_2H$$

The experimental realisation of each of the stages represented by equations I, II, IV, and V does not exclude the possibility that in the normal reaction some of these stages may be short-circuited or that other intermediates may be involved. For example, we find that distillation of a mixture of benzamide and benzenesulphonic acid affords phenyl cyanide and benzoic acid each in 95% yield according to the equation

$$2Ph\cdot CO\cdot NH_2 + Ph\cdot SO_3H \longrightarrow Ph\cdot CN + Ph\cdot CO_2H + Ph\cdot SO_2NH_4$$

and at a lower temperature dibenzoylamine may be isolated from the products of the reaction. Diacylamines are known to decompose on heating as follows

$$(R\cdot CO)_2NH \rightleftharpoons R\cdot CO\cdot O\cdot CR{:}NH$$
$$\searrow \quad \swarrow$$
$$R\cdot CN + R\cdot CO_2H$$

(see Mumm, Hesse, and Volquartz, *Ber.*, 1915, **48**, 379), and it is clear that they could be produced as intermediates in the reaction between carboxylic acids or anhydrides and sulphonamides, although we have not detected their formation. The fact that the optimum yield of phenyl cyanide is obtained from benzamide and benzenesulphonamide in presence of *ca.* 0·5 mol. of benzenesulphonic acid (above) may indicate that some dibenzoylamine is produced as an intermediate, but it will be appreciated that the ratio of benzamide to benzenesulphonamide throughout this reaction is higher than that which obtains at any stage of the reaction between benzenesulphonamide (2 mols.) and benzoic acid (I and II) which would therefore tend to produce benzoylbenzenesulphonamide. The available evidence strongly suggests that the main course of the reaction between a carboxylic acid and a sulphonamide follows equations (I)—(V).

Examples of the preparation of cyanides by this method are given in the Table. The influence of experimental conditions on the yield of cyanide has not been thoroughly investigated in all cases, so the yields recorded are not necessarily the highest obtainable. The method fails with acids which are readily decarboxylated (*e.g.*, *p*-hydroxybenzoic acid), and much decarboxylation occurs with anisic acid, which gives a poor yield of *p*-methoxyphenyl cyanide. It is convenient to employ benzene- and toluene-*p*-sulphonamides owing to their accessibility, although a somewhat lower yield (5%) of cyanide is usually obtained with toluenesulphonamide owing to the occurrence of a side reaction in which toluene is generated. There is usually no difficulty in regulating the experimental conditions so that very little amidine is formed when a cyanide is the desired product of the reaction. Thus, the maximum yield (75%) of *p*-cyanophenyl ethyl sulphone is obtained after 2—2½ hours at 210° and remains unaltered if the heating is prolonged for another 3 hours; at 225° a 75% yield of cyanide is obtained in 1½ hours and, although the yield falls to 30% after 10 hours owing to the production of *p*-amidinophenyl ethyl sulphone benzenesulphonate, rapid formation of the amidine salt does not occur until the temperature reaches 260—270°. Amidine formation occurs more readily in the case of *p*-chlorobenzoic acid, so that after 2 hours at 225° the product contains *p*-chlorophenyl cyanide (66%) and *p*-chlorobenzamidine benzenesulphonate (20%). A free sulphonic acid and its ammonium salt are produced in the reactions resulting in the formation of a cyanide and several examples are now recorded in which an increased yield of amidine salt is obtained if the sulphonic acid is neutralised with dry ammonia before raising the temperature to accelerate reaction V. This agrees with the conclusion (Part I, *loc. cit.*) that the yield of amidine salt is proportional to the concentration of the ammonium benzenesulphonate.

Cyanide.	Acid, g.	Benzenesulphonamide, g.	Benzenesulphonamide, mols.	Temp.	Time, hrs.	Yield, %.	M. p.
(1) Phenyl cyanide	12·2	31·4	2·0	220—225°	2·0	90	—
(2) *o*-Nitrophenyl cyanide	16·7	31·4	2·0	220—225	1·25	10·6	110°
(3) *p*-Nitrophenyl cyanide	16·7	31·4	2·0	225	1·0	81	148—149
(4) 2 : 4-Dinitrophenyl cyanide	21·2	32·0	2·0	205—210 and 225—230	1·0 and 1·0	79	103
(5) 3 : 5-Dinitrophenyl cyanide	42·4	64·0	2·0	225—230	1·75	83	127
(6) *p*-Chlorophenyl cyanide	25·0	50·0	2·0	225	2·0	66	95
(7) 2 : 4-Dichlorophenyl cyanide	19·0	39·3	2·5	225	2·0	80·7	60—61
(8) 2-*Cyanophenyl methyl sulphone*	25·0	39·25	2·0	225	1·5	83·5	103—104
(9) 3-Cyanophenyl methyl sulphone	50	78·5	2·0	225—230	1·25	61·0	103·5—104·5
(10) 4-Cyanophenyl methyl sulphone	20·0	31·4	2·0	225	1·5	75	142—143
(11) 4-Cyanophenyl ethyl sulphone	21·4	31·4	2·0	225	1·25	75	96
(12) 4-Cyanophenyl *n*-propyl sulphone	51·0	77·0	2·2	220—230	1·5	64	83—84
(13) 4 : 4′-Dicyanodiphenyl ether	6·5	15·7	4·0	220	1·5	*ca.* 45	180
(14) 4-*Cyanodiphenyl sulphone*	160	185	1·9	225	2·0	74	118
(15) 4 : 4′-Dicyanodiphenyl sulphone	40	210	10·0	225—230	2·0	76	229—231
(16) 4-*Cyanophenyl 4′-nitrobenzyl sulphone*	20·0	22·0	2·2	220—230	1·25	38	168—169
(17) Ammonium 4-cyanobenzenesulphonate	8·0	9·0	1·4	230—270	0·4	94	—
(18) *p*-Methoxyphenyl cyanide	15·2	31·4	2·0	220—225	7·0	10	60—61
(19) Benzyl cyanide	27·2	75·4	2·4	225	1·0	22	—

(1) The phenyl cyanide, b. p. 189—190°, was identified by the preparation of *m*-nitrophenyl cyanide, m. p. and mixed m. p. 117°. The preparation of larger batches and the use of other sulphonamides are described in the experimental section.

(2) The reaction was strongly exothermic. The product did not depress the m. p. of authentic *o*-nitrophenyl cyanide.

(3) The reaction is exothermic and the yield falls to 70% when 50 g. of acid are used.

(4) The reaction was conducted in stages to minimise decarboxylation. Friedländer and Cohn (*Ber.*, 1902, **35**, 1265; *Monatsh.*, 1902, **23**, 559) record 104—105° as the m. p. of 2 : 4-dinitrophenyl cyanide. Bennett and Wain (*J.*, 1936, 1108) give m. p. 99·6°.

(5) Bennett and Wain (*loc. cit.*) give m. p. 127°.

(6) Meyer (*Monatsh.*, 1917, **38**, 350) gives m. p. 94—96°. A 20% yield of p-*chlorobenzamidine benzenesulphonate*, m. p. 247° (Found: N, 8·95. $C_{13}H_{13}O_3N_2ClS$ requires N, 9·0%), was obtained as by-product. Dr. J. Cymerman found that the yield of cyanide after 1½ hours at 225° is 40% and that p-*chlorobenzamidine picrate* has m. p. 256° (decomp.) (Found: N, 18·1. $C_{13}H_{10}O_7N_5Cl$ requires N, 18·25%).

(7) Gomberg and Cone (*Annalen*, 1909, **370**, 182) give m. p. 61°.

(8) Preparation by Dr. J. W. Minnis. The cyanide (Found: N, 7·8. $C_8H_7O_2NS$ requires N, 7·7%) depressed the m. p. of 3-cyanophenyl methyl sulphone to 70—74°.

(9) Preparation by Dr. J. W. Minnis (Found: N, 7·75. Calc. for $C_8H_7O_2NS$: N, 7·7%). Fuller, Tonkin, and Walker (*J.*, 1945, 638) record m. p. 103—104°. Hydrolysis with 70% sulphuric acid gave *m*-carboxyphenyl methyl sulphone, m. p. and mixed m. p. 236—238°.

(10) Andrewes, King, and Walker (*Proc. Roy. Soc.*, 1946, *B*, **133**, 20) and Fuller, Tonkin, and Walker (*loc. cit.*) record m. p. 141°.

(11) The cyanide crystallised in glistening plates (Found: N, 7·2. Calc. for $C_9H_9O_2NS$: N, 7·2%). Fuller *et al.* (*loc. cit.*) record m. p. 94—95°.

(12) The cyanide separated from alcohol in colourless prisms (Found: N, 6·8. Calc. for $C_{10}H_{11}O_2NS$: N, 6·7%). Fuller *et al.* (*loc. cit.*) record m. p. 84—85°.

(13) The sulphonamide was mixed with 5% of benzenesulphonic acid. Ashley, Barber, Ewins, Newbery, and Self (*J.*, 1942, 113) also record m. p. 180°.

(14) Found: N, 5·8. $C_{13}H_9O_2NS$ requires N, 5·75%. Preparation by Dr. A. Koebner.

(15) Ashley *et al.* (*loc. cit.*) record m. p. 232—233°. Preparation by Dr. A. Koebner.

(16) Found: N, 9·3. $C_{14}H_{10}O_4N_2S$ requires N, 9·3%. Preparation by Dr. A. Koebner.

(17) The guanidine and the *p*-toluidine salt, obtained from the ammonium salt by double decomposition, melted at 236—237° and 241° respectively, and there was no depression on admixture with the appropriate salt prepared from authentic *p*-cyanobenzenesulphonic acid (Remsen, Hartman, and Muckenfuss, *loc. cit.*).

(18) Sulphur dioxide and carbon dioxide were evolved.

(19) The benzyl cyanide had b. p. 232—235°.

Experimental.*

Preparation of Acids.

o-*Carboxyphenyl Methyl Sulphone.*†—A solution containing *o*-mercaptobenzoic acid (15·4 g.) and sodium hydroxide (4 g.) in water (230 c.c.) was stirred during the addition of methyl sulphate (16 c.c.; 1·7 mols.) and a solution of sodium hydroxide (6 g.; 1·5 mols.) in water (20 c.c.). Methylation was completed by heating on the steam-bath for 2·5 hours, and the hot, filtered solution was acidified with concentrated hydrochloric acid. The yield of *o*-methylthiobenzoic acid, m. p. 168—169°, was 15 g. or 89% (cf. Friedländer, *Annalen*, 1907, **351**, 401). A solution of *o*-methylthiobenzoic acid (8·4 g.) and sodium hydroxide (2 g.; 1 mol.) in water (60 c.c.) was stirred mechanically and potassium permanganate (12 g.; equivalent to 2·3 atoms of oxygen) was added during 4 hours. After the excess of permanganate had been destroyed by sulphur dioxide the *o*-carboxyphenyl methyl sulphone was isolated in the usual way and dried at 110° for 1·5 hours; yield, 7·3 g., 73%; m. p. 134—135° (Found: S, 16·3; *M*, by titration, 199. Calc. for $C_8H_8O_4S$: S, 16·0%; *M*, 200). Arndt, Korsch, and Nachtwey (*Ber.*, 1926, **59**, 1079) record m. p. 138—140° (softening at 135°); Rule and Smith (*J.*, 1931, 1488) give m. p. 137°. In agreement with the latter authors we find that the monohydrate has m. p. 73°.

m-*Carboxyphenyl Methyl Sulphone.*†—A solution of crystalline sodium sulphite (540 g.; 2 mols.) in water (1 l.) was

* See also Boots Pure Drug Co., Oxley, Robson, Koebner, and Short, B.P. Appln., 21760/6.11.1944.

† Preparations by Dr. J. W. Minnis.

warmed to 70—80° and slowly added with stirring to a solution of *m*-chlorosulphonylbenzoic acid (220 g.; Smiles and Stewart, *J.*, 1921, **119**, 1792) in acetone (550 c.c.), concentrated aqueous sodium carbonate being added simultaneously so that the liquid remained alkaline to Brilliant-yellow. The reaction was completed by warming for 1·5 hours, and the sulphinic acid was precipitated by acidifying the solution at 0°. Sodium carbonate was added to a mixture of the crude sulphinic acid, alcohol (1 l.), and water (1 l.) until the solution was alkaline to Brilliant-yellow; methyl iodide (62 c.c.; 1 mol.) was then added, and the mixture boiled for 2 hours. After removal of most of the alcohol by distillation, the hot residue was filtered, and the filtrate acidified. The *m*-carboxyphenyl methyl sulphone was collected, washed, and dried at 60°. Yield, 106 g., 53%. The acid had m. p. 236—238°; Smiles and Stewart (*loc. cit.*) give m. p. 230°.

p-*Nitrophenyl Methyl Sulphone.*—The following modification of Waldron and Reid's method (*J. Amer. Chem. Soc.*, 1923, **45**, 2400) is more convenient and gives better yields. A solution of potassium hydrogen sulphide, prepared from potassium hydroxide (102 g.; 1·3 mols.), alcohol (400 c.c.), and hydrogen sulphide, was added to a hot solution of *p*-chloronitrobenzene (189 g.) in alcohol (750 c.c.) so that the solution boiled gently, air having been displaced from the apparatus by a current of nitrogen. The solution was boiled for a further 15 minutes and then poured into ice-water (6 l.). After standing at 0° for 2 hours the 4 : 4′-dinitrodiphenyl disulphide was removed and washed with water. The united filtrates were stirred during the slow addition of methyl sulphate (150 g.; 1 mol.), aqueous sodium hydroxide being added so that the liquid remained alkaline to Brilliant-yellow. Stirring was continued for 2 hours and the crude *p*-nitrothioanisole, m. p. 65—70°, was then collected; yield, 125 g., 61·7%. A sample recrystallised from aqueous acetic acid had m. p. 72° as described by Waldron and Reid (*loc. cit.*). Oxidation with concentrated nitric acid afforded p-*nitrophenyl methyl sulphoxide*, which separated from water in flat needles, m. p. 155° (Found : N, 7·7. $C_7H_7O_3NS$ requires N, 7·6%). The sulphone was obtained by dissolving the sulphide (50 g.) in acetic acid (250 c.c.) and water (30 c.c.) at 50° and adding potassium permanganate (55 g.; equivalent to 3 atoms of oxygen) with cooling so that the temperature remained at 55—60°. Acetic acid (100 c.c.) was then added, and after the colour had been discharged with sulphur dioxide, the solid was removed, and the filtrate concentrated under diminished pressure. *p*-Nitrophenyl methyl sulphone, m. p. 139° (45 g., 82%), was obtained by crystallising the residue from water and recrystallisation from alcohol afforded needles, m. p. 142°. Waldron and Reid (*loc. cit.*) record m. p. 142·5°.

p-*Aminophenyl Methyl Sulphone.*—A solution of the sulphone (20 g.) in alcohol (500 c.c.) containing Raney nickel (5 g.) was shaken in hydrogen at 50—70 lb./sq. in., reduction being complete in less than an hour. The yield of *p*-aminophenyl methyl sulphone, m. p. 134°, was 15·5 g., 90%. Waldron and Reid (*loc. cit.*) obtained a 70% yield of a product, m. p. 133°, by iron-reduction. Fuller, Tonkin, and Walker (*loc. cit.*), who obtained this amine from *p*-acetamidobenzenesulphinic acid, give m. p. 133—134°.

p-*Cyanophenyl Methyl Sulphone.*—(1) Sodium toluene-*p*-sulphinate was obtained in almost quantitative yield by adding toluene-*p*-sulphonyl chloride (200 g.) and sodium bicarbonate (175 g.; 2 mols.) during 2 hours to a solution of crystalline sodium sulphite (500 g.; 1·9 mols.) in water (1 l.) which was stirred and maintained at 70—80° during the addition and for 1 hour subsequently. The sodium salt was collected by filtration at 35—40° (cf. Blomstrand, *Ber.*, 1870, **3**, 965). The crude sodium salt was dissolved in water (500 c.c.) and alcohol (500 c.c.) and boiled for 12 hours with methyl iodide (87·4 c.c.; 1·3 mols.). Unchanged methyl iodide (30 g.) was recovered by distillation, and after concentration to a small volume under diminished pressure, the solid which separated was extracted with benzene (500 c.c.). The solution was washed with water and concentrated, giving 152—161 g. (85—90%) of *p*-tolyl methyl sulphone, m. p. 89—90°. Otto (*Ber.*, 1885, **18**, 161; *Annalen*, 1895, **284**, 304) records m. p. 86—87°. Potassium permanganate (340 g., equivalent to 3·2 atoms of oxygen) was added in portions during 4—5 hours to a suspension of *p*-tolyl methyl sulphone (170 g.) in water (1 l.) maintained at 90°. When decolorisation was complete *p*-carboxyphenyl methyl sulphone, m. p. 275°, was isolated in the usual way; yield, 185—190 g., 93—95%. Fuller, Tonkin, and Walker (*J.*, 1945, 633) state that this acid has m. p. 267—268°. The acid was converted into *p*-cyanophenyl methyl sulphone, m. p. 142—143°, by heating with benzenesulphonamide as described in the Table. (2) *p*-Aminophenyl methyl sulphone was diazotised and the solution added to sodium nickel cyanide as described by Fuller, Tonkin, and Walker (*loc. cit.*), the yield of *p*-cyanophenyl methyl sulphone being 71% as stated by them.

p-*Carboxyphenyl Ethyl Sulphone.*—This sulphone was prepared from sodium toluene-*p*-sulphinate by the method described in the case of the lower homologue. *p*-Tolyl ethyl sulphone (yield 74%), m. p. 56° (Otto, *loc. cit.*, gives m. p. 55—56°), was oxidised to *p*-carboxyphenyl ethyl sulphone, m. p. 220° (yield, 71%). Monier-Williams (*J.*, 1906, **89**, 279) gives m. p. 211°.

p-*Carboxyphenyl* n-*Propyl Sulphone.**—*p*-Tolyl *n*-propyl sulphone, m. p. 53—55°, was obtained in 75·5% yield from sodium toluene-*p*-sulphinate and propyl bromide in aqueous alcohol (cf. Otto, *J. pr. Chem.*, 1889, **40**, 562 Anm.). Addition of potassium permanganate (185 g.: equiv. to 3 atoms of oxygen) to a suspension of the sulphone (116 g.) in water (600 c.c.) at 90° during 12 hours afforded unchanged sulphone (20 g.) and 52 g. (47%) of crude acid, m. p. 190°. p-*Carboxyphenyl* n-*propyl sulphone* crystallised from 50% aqueous alcohol in colourless prisms, m. p. 191—193° (Found : C, 52·5; H, 5·3. $C_{10}H_{12}O_4S$ requires C, 52·6; H, 5·3%).

p-*Carboxyphenyl* p′-*Nitrobenzyl Sulphone.**—A solution of sodium toluene-*p*-sulphinate (65 g.) and *p*-nitrobenzyl chloride (65 g.; 1·04 mols.) in alcohol (65 c.c.) and water (150 c.c.) was boiled under reflux for an hour and afforded *p-tolyl* p′-*nitrobenzyl sulphone* (60 g., 56·5%), m. p. 185—189° (Found : N, 5·0. $C_{14}H_{13}O_4NS$ requires N, 4·8%). Concentrated sulphuric acid (35 c.c.) was added to a boiling solution of *p*-tolyl *p*′-nitrobenzyl sulphone (60 g.) and crystalline sodium dichromate (65 g., equiv. to 3·2 atoms of oxygen) in boiling acetic acid (300 c.c.) so that the mixture remained in gentle ebullition, and after a further hour's boiling the acid was collected, washed with hot water, and purified through the ammonium salt. p-*Carboxyphenyl* p′-*nitrobenzyl sulphone* had m. p. 295—300° (Found : N, 4·5. $C_{14}H_{11}O_6NS$ requires N, 4·4%); yield, 45 g., 68%.

Preparation of Carbonamides.

Benzdimethylamide.—When a mixture of benzoic acid (6·1 g.) and benzenesulphondimethylamide (9·25 g.; 1·0 mol.) was heated at 235—240° an exothermic reaction set in after about 5 minutes and the temperature rose to 250°, falling to 235—240° during the next 10 minutes. The product, which was completely soluble in a small quantity of water, was neutralised to Congo-red with aqueous potassium hydroxide (1·0 mol. required) and then extracted with benzene. The residue obtained by evaporating the washed and dried benzene solution was distilled and afforded 6·2 g. (83%) of a fraction, b. p. 132—133°/15 mm., which solidified on cooling and had m. p. 43°, undepressed on admixture with authentic benzdimethylamide (Kon and Staudinger, *Annalen*, 1911, **384**, 114).

Nicotinamide Benzenesulphonate.—Nicotinic acid (12·3 g.) and benzenesulphonamide (31·4 g.; 2 mols.) were kept at 225° for 4·5 hours, and the product extracted with acetone. The soluble solid afforded benzenesulphonamide (9 g.) after washing with aqueous sodium carbonate. The insoluble portion (17·5 g.) was recrystallised from ethyl alcohol–acetone, giving *nicotinamide benzenesulphonate*, m. p. 157° (Found : N, 10·1. $C_{12}H_{12}O_4N_2S$ requires N, 9·9%). Guanidine benzenesulphonate, m. p. and mixed m. p. 210—212°, was precipitated when guanidine sulphate was added to an aqueous solution

* Experiments by Dr. A. Koebner.

of the reaction product, and nicotinamide, m. p. 128—129°, was obtained by extracting the alkaline solution with chloroform. The product of the reaction did not depress the m. p. of a sample of nicotinamide benzenesulphonate, m. p. 157°, prepared from equivalent amounts of the amide and sulphonic acid in acetone.

Nicotinodiethylamide (*Nikethamide*).—(1) Nicotinic acid (12·3 g.) and benzenesulphondiethylamide (23·5 g.; 1·1 mols.) were kept at 225° for 3 hours, then dissolved in water (25 c.c.) and extracted with chloroform. The aqueous solution was made alkaline with 5N-sodium hydroxide and extracted with chloroform (2 × 50 c.c.) to give 8·8 g. (49·5%) of nikethamide, b. p. 115°/0·4 mm. (2) Nicotinic acid (12·3 g.) and toluene-*p*-sulphondiethylamide (25 g.; 1·1 mols.), heated at 250° for 1 hour, gave a 33% yield of nikethamide. (3) An 81% yield of nikethamide, b. p. 126—127°/mm., was obtained by heating nicotinic acid benzenesulphonate (7 g.) and benzenesulphondiethylamide (6 g.; 1·1 mol.) at 220° for 1 hour. *Nicotinic acid benzenesulphonate* was obtained from equivalent amounts of its constituents in hot acetone, and separated in white plates, m. p. 160° (Found: N, 5·1. $C_{12}H_{11}O_5NS$ requires N, 5·0%).

p-*Carbamylphenyl Methyl Sulphone*.—When a mixture of *p*-carboxyphenyl methyl sulphone (20 g.), benzenesulphonamide (16 g.; 1·02 mols.), and pyridine (7·9 g.; 1·0 mol.) was boiled under reflux for 3½ hours the b. p. rose from 200° to 280°. The product was extracted successively with aqueous sodium carbonate and aqueous sodium hydroxide, which removed unchanged acid (12·9 g.) and benzenesulphonamide (2·5 g.), respectively. The residual solid was recrystallised from water and afforded p-*carbamylphenyl methyl sulphone*, m. p. and mixed m. p. 226—226·5° (Found: N, 7·2. $C_8H_9O_3NS$ requires N, 7·0%); yield, 6·7 g., or 95% on the acid consumed.

N-*Acylbenzenesulphonamides*.

p-*Aminobenzenesulphonylacetamide* (*Sulphacetamide*).—When sulphacetamide (21·2 g.) was heated at 230° and finally over a free flame and the distillate was redistilled, methyl cyanide, b. p. 76—80°, was obtained in 49% yield (identified by hydrolysis to acetic acid).

Benzoylbenzenesulphonamide.—(1) Sodium (5·75 g.; 1 atom) was stirred with a warm solution of benzamide (30·25 g.) in xylene (200 c.c.) and, when the metal had disappeared, benzenesulphonyl chloride (44·1 g.; 1 mol.) was introduced, and the mixture stirred at room temperature until it was no longer alkaline (5 hours). The product was filtered and the xylene solution afforded benzenesulphonyl chloride, b. p. 113°/9 mm. (20 g.). Benzoylbenzenesulphonamide, m. p. 147—147·2° (16 g.), was obtained from the solid by dissolving it in water, acidifying with dilute hydrochloric acid, and recrystallising the precipitate from alcohol. The benzoylbenzenesulphonamide was evidently converted into its sodio-derivative (by the sodio-benzamide), which did not react with the sulphonyl chloride. The mixed imide did not depress the m. p. of samples prepared by heating benzoyl chloride and benzenesulphonamide either alone at 135° for 3 hours (cf. Wallach, *loc. cit.*) or in presence of pyridine (1 mol.) at 95° for 2 hours.

(2) Benzamide (4·8 g.), benzenesulphonamide (6·25 g.; 1 mol.), and anhydrous benzenesulphonic acid (6·3 g.; 1 mol.) were heated at 155° for 3 hours and extracted with aqueous sodium bicarbonate. Acidification of the solution afforded benzoylbenzenesulphonamide (0·3 g., 3%), m. p. and mixed m. p. 147°. When benzoylbenzenesulphonamide (10 g.) was heated at 200°, there was a sudden exothermic reaction after *ca.* 30 minutes and the temperature soon fell to 190° owing to vigorous refluxing of phenyl cyanide. The reaction product consisted of phenyl cyanide (3·5 g., 89%) and benzenesulphonic acid (82% by titration), identified respectively as *m*-nitrophenyl cyanide, m. p. and mixed m. p. 117°, and guanidine benzenesulphonate, m. p. and mixed m. p. 211°.

N-p-*Methylsulphonylbenzoylbenzenesulphonamide*.—(1) Two tubes were each charged with *p*-carboxyphenyl methyl sulphone (10 g.) and benzenesulphonamide (15·7 g.; 2 mols.), and anhydrous benzenesulphonic acid (0·5 g.) was added to one of them. The tubes were heated in a bath at 225° for 70 minutes and then cooled rapidly. An exothermic reaction temporarily raised the internal temperature *ca.* 5° above that of the bath, and this phase occurred sooner in the tube containing the sulphonic acid. The powdered products were worked up separately by stirring with water, adding ammonia until alkaline to Brilliant-yellow, collecting the *p*-cyanophenyl methyl sulphone, m. p. 140—141°, and recrystallising it once from alcohol, whereupon the m. p. rose to 142·4—142·8°. Acidification of the ammoniacal solution and recrystallisation of the precipitate from alcohol afforded N-p-*methylsulphonylbenzoylbenzenesulphonamide*, which crystallised in long needles, m. p. 214·6—215° (Found: C, 50·2; H, 4·1; N, 4·2. $C_{14}H_{13}O_5NS_2$ requires C, 49·6; H, 3·8; N, 4·1%). The yields of cyanide and mixed imide in the experiment without added sulphonic acid were 5·62 g. (62%) and 3·5 g. (20·6%), respectively. In the experiment with added sulphonic acid, the corresponding figures were 7·27 g. (80·3%) and 0·2 g. (1·2%), respectively.

(2) *p*-Carboxyphenyl methyl sulphone (10 g.) and thionyl chloride (20 c.c.) were boiled for 3 hours, excess of thionyl chloride was removed by distillation under diminished pressure, and the crude acid chloride, m. p. 131°, was mixed with benzenesulphonamide (8 g.) and heated at 145° for 3½ hours. The product was recrystallised from alcohol, giving 4·6 g. (50·8%) of the mixed imide, m. p. 214—215°.

(3) An equimolecular mixture of *p*-carbamylphenyl methyl sulphone (3·0 g.), benzenesulphonamide (2·4 g.), and benzenesulphonic acid (2·4 g.) was kept at 198° for ½ hour and afforded 2·2 g. (81%) of *p*-cyanophenyl methyl sulphone and 0·4 g. (8%) of the mixed imide.

When *p*-methylsulphonylbenzoylbenzenesulphonamide (4 g.) was kept at 230° for 1 hour, and the product washed with dilute aqueous ammonia, *p*-cyanophenyl methyl sulphone, m. p. 138—140° (2·03 g., 95%), remained, and crystallisation from alcohol raised the m. p. to 142·5°.

N-p-*Ethylsulphonylbenzoylbenzenesulphonamide*.—*p*-Carboxyphenyl ethyl sulphone (21·4 g.) and benzenesulphonamide (31·4 g.; 2 mols.) were heated to 225° in 6 minutes, stirred at this temperature for 30 minutes, and cooled quickly. Crude ammonium benzenesulphonate (13·9 g., 79%), m. p. 270—283°, remained undissolved when the melt was extracted with acetone, and recrystallisation from aqueous acetone (charcoal) afforded glistening white plates, m. p. and mixed m. p. 285—286°, of the pure salt (Found: N, 7·9, 7·95, 8·2. Calc. for $C_6H_9O_3NS$: N, 8·0%). The ammonium salt was converted into *p*-toluidine benzenesulphonate, m. p. and mixed m. p. 203°, by reaction with *p*-toluidine hydrochloride. The acetone-soluble product was extracted successively with saturated aqueous sodium bicarbonate and dilute sodium hydroxide solution, and the residue (12·5 g., m. p. 95°) afforded 11·5 g. (59%) of pure *p*-cyanophenyl ethyl sulphone, m. p. 95—96°, on recrystallisation from aqueous alcohol. The sodium bicarbonate solution was concentrated and acidified, and the precipitate (4·5 g., 12·7%) on recrystallisation from hot water gave N-p-*ethylsulphonylbenzoylbenzenesulphonamide*, which crystallised in small needles, m. p. 189° (Found: N, 4·0, 4·0. $C_{15}H_{15}O_5NS_2$ requires N, 4·0%).

N-p-*Nitrobenzoylbenzenesulphonamide*.—(1) *p*-Nitrobenzoyl chloride (4·65 g.) and benzenesulphonamide (3·95 g.; 1 mol.) were heated at 145—150° for 5 hours and boiled with alcohol (20 c.c.) to destroy acid chloride. The solvent was removed and the powdered product was suspended in water and made alkaline to Brilliant-yellow with sodium carbonate. The filtered solution was acidified, and the precipitate, m. p. 212—214° (4·6 g., 60%), recrystallised from methanol, giving N-p-*nitrobenzoylbenzenesulphonamide*, m. p. 216—217° (Found: N, 9·1. $C_{13}H_{10}O_6N_2S$ requires N, 9·15%).

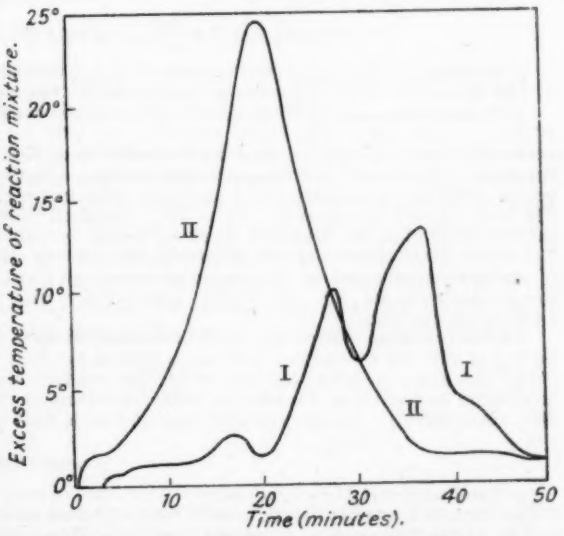
(2) A mixture of *p*-nitrobenzoic acid (6·7 g.) and benzenesulphonamide (12·6 g.) was heated to 220° in 3 minutes, and the tube containing the melt was then placed in the vapour of boiling methyl salicylate. The melt was stirred, and the temperatures of the melt and of the vapour bath were recorded at minute intervals on calibrated thermometers. The

temperature of the bath remained constant to within 0·5° throughout, and the results are shown in the Fig., in which the difference between the temperatures of the reaction mixture and the bath is plotted against the time. [The second curve was obtained when the experiment was repeated in presence of benzenesulphonic acid monohydrate (0·2 g.) and shows the acceleration produced by the acid.] It was assumed that the mixed imide is mainly produced during the first 20 minutes, and that its decomposition into cyanide and sulphonic acid is responsible for the subsequent strongly exothermic phase. The experiment was repeated on the same scale, but the tube was cooled rapidly in water 19 minutes after the temperature of the mixture attained that of the vapour bath. The powdered product was warmed with acetone (50 c.c.) and kept overnight at 0°. The solid was collected, washed with acetone (50 c.c.), and filtered, giving a solid (A), and the acetone solutions were united (B). The solid (A) was resolved by water (20 c.c.) into ammonium benzenesulphonate (2·6 g.), m. p. and mixed m. p. 279°, and *p*-nitrobenzoic acid (1·4 g.), m. p. and mixed m. p. 240°. The acetone solution (B) was diluted with water (20 c.c.), distilled to remove acetone, cooled to 50°, and rendered alkaline to Brilliant-yellow with sodium carbonate; after cooling to room temperature, the solid was collected and washed thoroughly with water. The washings were added to the sodium carbonate solution (C). The solid was separated by means of 1·7N-sodium hydroxide (15 c.c.) into benzenesulphonamide, m. p. 153—154° (4·4 g.), and *p*-nitrophenyl cyanide, m. p. 148—149° (0·8 g.). The sodium carbonate solution (C) was concentrated to 25 c.c. and acidified with hydrochloric acid, and the solid was collected, washed with a little water, and dried. This solid was extracted with hot chloroform (50 c.c. and 3 × 20 c.c.) leaving *p*-nitrobenzoic acid, m. p. 235—237° (1·0 g.). The chloroform extract was purified by crystallisation from ethanol and gave *N*-*p*-nitrobenzoylbenzenesulphonamide (4·4 g.), m. p. and mixed m. p. 213—215°. These results may be summarised as follows:

	Initial.	Recovered.	Reacted.
Benzenesulphonamide, g.-mol.	0·080	0·028	0·052
p-Nitrobenzoic acid, g.-mol.	0·0400	0·0144	0·0256

The ratio of acid to sulphonamide entering into reaction was therefore 1 : 2·03. The yield of cyanide was 0·0054 g.-mol., so that 0·0202 g.-mol. of acid was converted into mixed imide, 0·0140 g.-mol. of which was isolated, together with 0·015 g.-mol. of ammonium benzenesulphonate.

Decomposition of *N*-*p*-nitrobenzoylbenzenesulphonamide (5 g.) at 220° for 40 minutes gave *p*-nitrophenyl cyanide (81%), benzenesulphonic acid (86%, isolated as ammonium salt), and unchanged imide (1·4%). The reaction was first exothermic then endothermic and finally exothermic, the curve having the same shape as the final portion of that representing the reaction between *p*-nitrobenzoic acid and benzenesulphonamide (Fig.). It was found that a 66% yield of cyanide is obtained if heating is interrupted after the first exothermic reaction (18 minutes), and the significance of the subsequent endothermic phase is at present obscure.



I. p-*Nitrobenzoic acid and benzenesulphonamide.*
II. p-*Nitrobenzoic acid, benzenesulphonamide, and benzenesulphonic acid.*

N-o-*Nitrobenzoylbenzenesulphonamide.*—*o*-Nitrobenzoic acid (6·68 g.) and benzenesulphonamide (12·56 g.; 2 mols.) were heated in a bath at 225°, and as soon as the internal temperature reached 230° (24 minutes), the reaction was arrested by cooling in ice. The product, separated by the method used in the case of the *p*-acid, consisted of benzenesulphonamide (8·3 g.), *o*-nitrobenzoic acid (3·5 g.), ammonium benzenesulphonate (2·09 g.), and *N*-o-*nitrobenzoylbenzenesulphonamide* (2·73 g.), which separated from aqueous alcohol in glistening leaflets, m. p. 171° (Found: N, 9·3. $C_{13}H_{10}O_5N_2S$ requires N, 9·15%). The yield of imide was 46% on the acid consumed, or 64% on the sulphonamide consumed. When *N*-*o*-nitrobenzoylbenzenesulphonamide (2 g.) was heated in a bath at 225° and cooled quickly in ice as soon as the temperature of the melt rose sharply (8 minutes), the product contained *o*-nitrophenyl cyanide (0·16 g.), unchanged imide (1·2 g.), and benzenesulphonic acid, isolated as ammonium salt (0·21 g.); the yields of cyanide and sulphonic acid are 42 and 45·8%, respectively, calculated on the imide consumed. The temperature changes which occur during the interaction of *o*-nitrobenzoic acid and benzenesulphonamide were also recorded: the general features were similar to those observed in the case of the *p*-isomer, except that the second stage (decomposition of the imide) is much more strongly exothermic, so this part of the curve shows no inflexion. A considerable amount of tar is produced during the decomposition of the imide and impedes the isolation of pure *o*-nitrophenyl cyanide from the product.

Preparation of Cyanides.

Phenyl Cyanide.—(1) *From benzoic acid.* (*a*) Benzoic acid (122 g.) and technical benzenesulphonamide (314 g.; 2 mols.) were stirred at 220—225° for 2 hours under reflux and then distilled (bath up to 300°). The distillate was diluted with ether (25 c.c.), washed with dilute alkali and water, and dried. The fraction, b. p. 189—193°, was collected as phenyl cyanide; yield, 69 g., 67%. (*b*) Benzoic acid (122 g.), toluene-*p*-sulphonamide (342 g.; 2 mols.), and toluene-*p*-sulphonic acid monohydrate (10 g.) were heated at 240° and stirred. After 10—20 minutes, an exothermic reaction raised the temperature of the melt to *ca.* 250° and vigorous refluxing occurred. The product was then distilled under diminished pressure (100 mm.), and the distillate afforded phenyl cyanide, b. p. 188—196° (mainly 190—193°), on redistillation; yield, 74 g., 72%.

(2) *From benzoic anhydride.* Benzoic anhydride (4·5 g.) and benzenesulphonamide (9·5 g.; 3 mols.) reacted vigorously when heated at 240° for 15 minutes. The product was shaken with water, the dissolved benzenesulphonic acid titrated with alkali, and the phenyl cyanide separated. The yield of cyanide was 3·5 g. (85%), and 95% of the calculated amount of benzenesulphonic acid was produced.

(3) *From benzamide.* (*a*) A mixture of benzamide (7·26 g.) and anhydrous benzenesulphonic acid (10 g.) was heated at 280—315° so that the products distilled. The distillate, b. p. 235—236°, consisted of benzoic acid, m. p. and mixed m. p. 121° (3·5 g., 95%), and phenyl cyanide, b. p. 189—190° (2·9 g., 95%), identified as *m*-nitrophenyl cyanide, m. p. and mixed m. p. 117°.

(*b*) Benzamide (7 g.), benzenesulphonamide, and anhydrous benzenesulphonic acid (9·2 g.; 1 mol.), heated at 235° for 20 minutes, afforded ammonium benzenesulphonate (insoluble in acetone) and phenyl cyanide. The yield varied with the amount of benzenesulphonic acid as follows:

Benzenesulphonic acid (mols.)	0·04	0·25	0·5	1·0
Phenyl cyanide, %	Trace	25	53	74
Ammonium benzenesulphonate, %	Trace	25	78	77

If the reaction is carried out at a lower temperature the product also contains benzoylbenzenesulphonamide (see above).

(*c*) A mixture of benzamide (5·1 g.), benzenesulphondimethylamide (7·85 g.; 1 mol.), and anhydrous benzenesulphonic acid (6·7 g.; 1 mol.) was heated at 230—235° for 20 minutes. The product, which was completely soluble in acetone (absence of ammonium benzenesulphonate), was dissolved in *iso*propanol, and the solution on inoculation deposited dimethylammonium benzenesulphonate (6·5 g., 75%), m. p. and mixed m. p. 116°. Norton and Westenhoff (*Amer. Chem. J.*, 1888, **10**, 13) record m. p. 110°. The filtrate contained 3·5 g. (82%) of phenyl cyanide.

(*d*) Benzamide (6·05 g.) and benzamide benzenesulphonate (13·95 g.; 1 mol.) were heated at 160° for 2 hours and then dissolved in chloroform. Extraction with aqueous sodium bicarbonate afforded benzoic acid, m. p. 118—120° (1·1 g., 18%), and aqueous sodium hydroxide removed dibenzoylamine, m. p. 146—147° (1·5 g., 13·5%). The chloroform was removed by distillation, and the residue afforded benzamide, m. p. 125—127° (8·0 g., 66%), when triturated with benzene, and the benzene solution afforded crude phenyl cyanide (1·2 g., 23%) containing some benzamide.

(*e*) A 78% yield of phenyl cyanide was obtained when a mixture of benzamide (6·05 g.) and benzenesulphonyl chloride (8·8 g.; 1 mol.) was heated at 125—130° for ½ hour. The cyanide was isolated from a solution of the reaction product in dry benzene after 12 hours' keeping and removal of a solid (2 g.) by filtration. Recrystallisation from benzene gave slender needles of *benzamide benzenesulphonate*, m. p. 121·5—122° (Found: C, 56·0; H, 4·7; N, 5·2; *M*, by titration, 280. $C_{13}H_{13}O_4NS$ requires C, 55·9; H, 4·7; N, 5·0%; *M*, 279). This salt, which was also obtained from its constituents in chloroform solution, was decomposed by aqueous sodium carbonate with liberation of benzamide, m. p. and mixed m. p. 128°. Benzoic acid and phenyl cyanide were produced when the salt was heated at 225°:

$$2Ph\cdot CO\cdot \overset{\oplus}{N}H_3\}\overset{\ominus}{SO_3}Ph \longrightarrow Ph\cdot CN + Ph\cdot CO_2H + Ph\cdot SO_3H + Ph\cdot SO_3NH_4.$$

p-*Nitrophenyl Cyanide.*—*p*-Nitrobenzoic anhydride (26·5 g.) and toluene-*p*-sulphonamide (43 g.; 3 mols.), heated at 225° for ½ hour, afforded *p*-nitrophenyl cyanide (16 g., 64·5%), m. p. 149°.

p-*Cyanobenzenesulphonic Acid.*—*p*-Sulphonamidobenzoic acid (8 g.) and benzenesulphonamide (9 g.; 1·4 mols.) afforded a clear melt after being heated at *ca.* 230° for 15 minutes, and after a further 5—10 minutes there was an exothermic reaction which raised the temperature to 270°. The reaction product was triturated with acetone to remove benzenesulphonic acid and benzenesulphonamide, and the residual ammonium *p*-cyanobenzenesulphonate (7·5 g., 94%) was purified by recrystallisation from dilute ammonium chloride solution; m. p. above 290°. The guanidine salt, m. p. 236—237°, and *p*-toluidine salt, m. p. 241°, prepared from the ammonium salt by double decomposition, did not depress the m. p. of samples prepared from authentic *p*-cyanobenzenesulphonic acid (Remsen, Hartman, and Muckenfuss, *loc. cit.*). Ammonium *p*-cyanobenzenesulphonate was also prepared from *p*-sulphonamidobenzoic acid and 1—1·1 mols. of toluene-*p*-sulphonamide, benzenesulphonmethylamide, or benzenesulphondimethylamide under the same conditions, the yields being 94, 80, and 67·5%, respectively, and the reaction product was crystallised directly from aqueous ammonium chloride.

3-*Cyanopyridine.*—Nicotinic acid benzenesulphonate (14·05 g.) and benzenesulphonamide (19 g.; 2·4 mols.) were heated at 230° for 40 minutes and the powdered product was stirred with dry acetone. Ammonium benzenesulphonate (78%) remained undissolved, and when the residue obtained by evaporating the acetone solution was dissolved in 5N-sodium hydroxide and extracted with chloroform, 3-cyanopyridine, m. p. and mixed m. p. 49—50°, was obtained in 75% yield (9·8 g.). Its *benzenesulphonate* had m. p. 132° (Found: N, 10·6. $C_{12}H_{10}O_3N_2S$ requires N, 10·7%).

Preparation of Amidines.

p-*Amidinophenyl Methyl Sulphone.*—A mixture of *p*-carboxyphenyl methyl sulphone (14 g.) and benzenesulphonamide (22 g.; 2 mols.) was kept at 220—225° for 1·25 hours with mechanical stirring. Dry ammonia was then passed over the surface of the melt until no more was absorbed. The stream of gas was then stopped, and the temperature was raised to 255—260° during 10 minutes and kept thereat for 2 hours. The product was dissolved in hot water (42 c.c.), the solution then being cooled to 60° and poured into a mixture of ice (105 g.) and 36% aqueous sodium hydroxide (35 c.c.) with vigorous stirring. The precipitate was collected, washed with a little ice-water, suspended in water (52 c.c.), brought to pH 6·5 with hydrochloric acid, and filtered. The residue (2·2 g.) was *p*-cyanophenyl methyl sulphone, m. p. 139—142°, and sodium hydroxide precipitated the crude amidine (7·8 g.) from the filtrate. The amidine was washed with ice-water, suspended in water (90 c.c.), and brought to pH 6·5—7·0 with hydrochloric acid; the solution was stirred with charcoal (0·5 g.) and filtered, and the filtrate was evaporated to dryness on the steam-bath. The residue was powdered, washed with a little acetone, and dried at 100°, giving almost pure *p*-amidinophenyl methyl sulphone hydrochloride, m. p. 290—291° (7·84 g., 60%). The pure amidine hydrochloride has m. p. 294° (see Part I). The yield of amidine hydrochloride fell to 7·6 g. (48·7%) when the stream of ammonia was omitted, all other conditions remaining unaltered, and to 5·8 g. (35%) when toluene-*p*-sulphonamide was used in place of benzenesulphonamide.

p-*Amidinophenyl Ethyl Sulphone.*—(1) A mixture of *p*-carboxyphenyl ethyl sulphone (22 g.) and benzenesulphonamide (40 g.; 2·5 mols.) was melted and stirred at 235° ± 5° for 3 hours and the product was extracted with boiling acetone to remove *p*-cyanophenyl ethyl sulphone (7 g., 32%; m. p. 95°) and excess of benzenesulphonamide. The amidine was liberated from the residue and converted into the hydrochloride as described in the previous example. *p*-Amidinophenyl ethyl sulphone hydrochloride separated from aqueous acetone in rhombs, m. p. 253° (Found: N, 11·45. Calc. for $C_9H_{12}O_2N_2ClS$: N, 11·3%); yield, 12·5 g., 49%. Fuller, Tonkin, and Walker (*loc. cit.*) record m. p. 246—247°.

(2) *p*-Cyanophenyl ethyl sulphone (23 g.) and ammonium benzenesulphonate (25 g.; 1·2 mols.) were stirred at 245° for 4 hours and the powdered product was extracted with acetone to remove unchanged cyanide (8·9 g.). The residue was recrystallised from boiling water (75 c.c.) in presence of charcoal, giving 23 g. (52·5%) of p-*amidinophenyl ethyl sulphone benzenesulphonate*, which crystallised in plates, m. p. 240° (Found: N, 7·65. $C_{15}H_{16}O_5N_2S_2$ requires N, 7·6%).

p-*Nitrobenzamidine.*—Rouiller (*loc. cit.*) obtained *p*-nitrobenzamidine benzenesulphonate and *p*-nitrophenyl cyanide in 31 and 27% yield respectively by heating *p*-nitrobenzoic acid and benzenesulphonamide (2 mols.) at 220° for 5 hours, and we found that the yield could be increased by neutralising the sulphonic acid with ammonia. Thus, *p*-nitrobenzoic acid (3·34 g.) and benzenesulphonamide (6·28 g.) were kept at 220—225° for 1·25 hours, and, after passage of dry ammonia for 0·5 hour, the temperature was raised to 255—260° and kept thereat for 2 hours. The cooled reaction product was triturated with ice and 5N-sodium hydroxide (10 c.c.), and the solid was collected, washed with water, and neutralised with dilute hydrochloric acid. The insoluble portion afforded *p*-nitrophenyl cyanide, m. p. 149° (33%), when extracted with

acetone, and *p*-nitrobenzamidine, m. p. 213° (43·5%), was precipitated from the solution of the hydrochloride by adding 10N-sodium hydroxide. Pinner and Gradenwitz (*Annalen*, 1897, **298**, 47) record m. p. 215°. p-*Nitrobenzamidine picrate* had m. p. 240° (Found: N, 21·5. $C_{13}H_{10}O_9N_6$ requires N, 21·3%). *p*-Chlorobenzenesulphonamide was also used in the preparation of this amidine.

3 : 4-*Dichlorobenzamidine.*—A mixture of 3 : 4-dichlorobenzoic acid (3·82 g.) and benzenesulphonamide (6·28 g.; 2 mols.) was maintained at 220—225° for 1·75 hours, a stream of dry ammonia being passed over the melt during the last 0·5 hour, and the temperature was then kept at 260° for 2 hours. The powdered product was extracted with cold acetone (120 c.c.) which removed 3 : 4-dichlorophenyl cyanide, m. p. 70—71° (1·1 g., 29%). Kraay (*Rec. Trav. chim.*, 1930, **49**, 1084) states that 3 : 4-dichlorophenyl cyanide has m. p. 71·8—72·1°. The portion insoluble in acetone was washed with water and recrystallised from alcohol, giving 3·68 g. (53%) of 3 : 4-*dichlorobenzamidine benzenesulphonate*, m. p. 240—241° (Found: N, 8·2. $C_{13}H_{13}O_3N_3Cl_2S$ requires N, 8·1%). 3 : 4-*Dichlorobenzamidine* separated from benzene in leaflets, m. p. 94—95° (Found: N, 15·0. $C_7H_6N_2Cl_2$ requires N, 14·8%), and afforded a *hydrochloride* which crystallised from alcohol–ether in prisms, m. p. 239·5° (Found: N, 12·3. $C_7H_7N_2Cl_3$ requires N, 12·4%). When the preparation was carried out without introducing the stream of ammonia the yield of 3 : 4-dichlorobenzamidine benzenesulphonate fell to 35%.

4 : 4′-*Diamidinodiphenyl Ether.*—A mixture of 4 : 4′-dicarboxydiphenyl ether (2·58 g.), benzenesulphonamide (6·28 g.; 4 mols.), and benzenesulphonic acid (0·1 g.) was heated at 240° until a homogeneous melt was obtained (0·5 hour) and was then kept at 220—225° for 1 hour. After passage of dry ammonia at 220° for 15 minutes, the melt was kept at 260—265° for 2·25 hours, and the amidine, isolated in the usual way, had m. p. 213—214° (decomp.) alone or mixed with an authentic specimen (Ashley, *et al.*, *loc. cit.*); yield 1·05 g., 42%.

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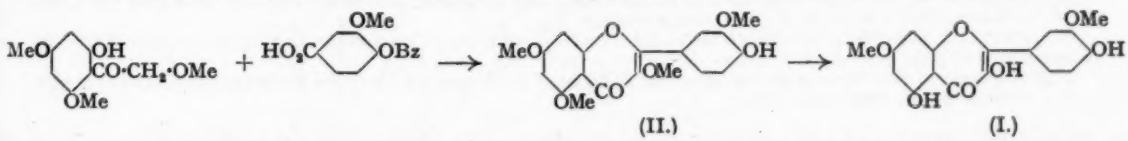
157. *Synthesis of Rhamnazin.*

BY KOPPAKA VISWESWARA RAO and TIRUVENKATA RAJENDRA SESHADRI.

The synthesis of rhamnazin (I) has been effected by condensing 2-hydroxy-ω : 4 : 6-trimethoxyacetophenone with the anhydride and sodium salt of benzoylvanillic acid and subjecting the tetramethyl ether of quercetin (II) thus obtained to partial demethylation with aluminium chloride in nitrobenzene solution.

RHAMNAZIN (I) occurs in Persian berries with rhamnetin and quercetin (Perkin and Geldard, *J.*, 1895, **67**, 500). Its constitution as the 7 : 3′-dimethyl ether of quercetin was established by Perkin and Allison (*J.*, 1902, **81**, 470). The synthesis has now been effected following in general the procedure adopted in the case of izalpinin (Rao and Seshadri, *Proc. Ind. Acad. Sci.*, 1945, **22**, A, 383). 2-Hydroxy-ω : 4 : 6-trimethoxyacetophenone is condensed with the anhydride and sodium salt of benzoylvanillic acid according to the method of Allan and Robinson. The resulting 3 : 5 : 7 : 3′-*tetramethyl ether* (II) of quercetin is subjected to partial demethylation using aluminium chloride in nitrobenzene solution. The synthetic compound has all the properties of rhamnazin and the identity has been confirmed by the preparation of the acetyl and benzoyl derivatives.



A new procedure has been adopted for the preparation of benzoylvanillic acid, by oxidising benzoylvanillin with potassium permanganate in acetic acid solution. The product is then obtained more readily pure and in better yields than by older methods (Tiemann and Kraaz, *Ber.*, 1882, **15**, 2068; Heap and Robinson *J.*, 1926, 2342) in which the separation of by-products causes difficulty.

EXPERIMENTAL.

Benzoylvanillic Acid and Anhydride.—Benzoylvanillin (10 g.) was dissolved in glacial acetic acid (100 c.c.) and aqueous potassium permanganate (7 g. in 150 c.c. of water) gradually added during the course of an hour with vigorous stirring, the temperature being kept at 70—80°. Precipitated manganese dioxide was dissolved by passing sulphur dioxide, and the solution treated with a large volume of water. The acid that separated was filtered off and washed with water. One crystallisation from alcohol yielded colourless prismatic needles, m. p. 174—176°; yield, 7 g. A second crystallisation raised the m. p. to 177—178°.

Dry pyridine (8 c.c.) was added to a solution of benzoylvanilloyl chloride (Heap and Robinson, *loc. cit.*) (5 g.) in anhydrous ether. After 2½ hours in the ice-chest, small pieces of ice and ice-cold dilute hydrochloric acid were added and the mixture was stirred vigorously; a pale cream coloured solid then separated. It was filtered off, washed with ice-cold hydrochloric acid followed by ice water, and dried in a vacuum desiccator; yield, 4 g.

4′-*Hydroxy*-3 : 5 : 7 : 3′-*tetramethoxyflavone* (II).—An intimate mixture of 2-hydroxy-ω : 4 : 6-trimethoxyacetophenone prepared by the partial methylation of 2 : 4 : 6-trihydroxy-ω-methoxyacetophenone (Row and Seshadri, *Proc. Ind. Acad. Sci.*, 1946, **23**, A, 23) (1 g.), benzoylvanillic anhydride (5 g.), and sodium benzoylvanillate (2 g.) was heated under vacuum at 180° for 3 hours. The solid cake was taken out, finely powdered, and refluxed with alcoholic potash (50 c.c. of 10% solution) till it completely dissolved. The solvent was then removed under reduced pressure and the solid residue dissolved in water (150 c.c.). The clear yellowish-brown solution was saturated with carbon dioxide. The yellow solid which separated was filtered off, washed, and crystallised from alcohol; yield, 1·2 g. After a second crystallisation it formed very pale yellow rectangular plates and prisms, m. p. 200—201° (Found: C, 63·8; H, 5·3. $C_{19}H_{18}O_7$ requires C, 63·7; H, 5·0%). The *compound* dissolved in aqueous sodium hydroxide or sodium carbonate to give a stable yellow colour. With ferric chloride it produced no characteristic colouration. Its solution in concentrated sulphuric acid had a yellow colour with green fluorescence.

A portion of the above compound (0·2 g.) was methylated by refluxing a solution in anhydrous acetone with methyl

sulphate (0·5 c.c.) and potassium carbonate (3·0 g.) for 6 hours. The methyl ether separated as colourless narrow rectangular plates, m. p. 152—153°. The mixed m. p. with an authentic sample of quercetin pentamethyl ether was not depressed.

The tetramethyl ether of quercetin (0·2 g.) was acetylated by boiling with acetic anhydride (3 c.c.) and a few drops of pyridine. The *acetate* was crystallised twice from alcohol from which it separated in colourless flat needles, m. p. 178—180° (Found: C, 62·9; H, 5·3. $C_{21}H_{20}O_8$ requires C, 63·0; H, 5·0%).

3 : 5 : 4′-*Trihydroxy*-7 : 3′-*dimethoxyflavone* (*Rhamnazin*).—The tetramethoxyflavone (II) (1·0 g.) was dissolved in dry nitrobenzene (8 c.c.), treated with a solution of anhydrous aluminium chloride (2 g.) in the same solvent (8 c.c.), and kept in a boiling water-bath for 1½ hours. The product was then cooled and excess of light petroleum added. The brown precipitate was filtered off, washed thoroughly with light petroleum, and dried. It was then treated with dilute hydrochloric acid, and the mixture heated nearly to boiling and filtered. The solid product was washed twice with hot alcohol (5 c.c.) to remove any unconverted original compound. The yellow residue (0·8 g.) was then crystallised from glacial acetic acid. Further purification was effected by crystallisation from toluene from which it separated in glistening pale yellow rectangular prisms, m. p. 215—216° (Found: C, 61·6; H, 4·4; OMe 19·3. Calc. for $C_{17}H_{14}O_7$: C, 61·8; H, 4·2; OMe, 18·8%).

The compound in alcoholic solution gave an olive-green colour with ferric chloride and an orange-red precipitate with alcoholic lead acetate. In aqueous alkali it dissolved to an orange solution. In concentrated suphuric acid it formed a yellow solution with a brilliant green fluorescence.

The compound (0·3 g.) was acetylated by boiling with acetic anhydride (3 c.c.) and a few drops of pyridine for 1 hour. The white solid that separated out on pouring the reaction mixture into water was collected, washed, and purified by crystallisation successively from alcohol and benzene–light petroleum. The pure acetate formed colourless narrow rectangular plates and flat needles, m. p. 154—155°.

Acetylrhamnazin (0·15 g.) was dissolved in alcohol (10 c.c.) and treated with concentrated hydrochloric acid (2 c.c.). The clear solution was heated on a water-bath for 10 minutes during which time a yellow crystalline solid separated. This was filtered off, washed with a little hot alcohol, and crystallised from toluene from which it separated in pale yellow rectangular prisms, m. p. 215—216°, identical with the original rhamnazin; yield, 0·1 g.

A solution of synthetic rhamnazin (0·1 g.) in aqueous sodium hydroxide was shaken vigorously with benzoyl chloride (0·5 c.c.) till the odour of the chloride disappeared. The solid benzoyl derivative was collected, washed with dilute alkali followed by water, and crystallised from ethyl acetate–light petroleum; it formed rectangular prisms, m. p. 205—207°; yield, 0·1 g.

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158. *A Study of the Reaction of Some Nitrosoamines with α-Naphthylamine Hydrochloride.*

By C. A. PARKER.

The colorimetric reaction between aromatic *N*-nitrosoamines and α-naphthylamine hydrochloride takes place by the liberation of the nitroso-group and its reaction with α-naphthylamine hydrochloride to give the blue-violet hydrochloride of 4-amino-1 : 1′-azonaphthalene.

The reaction is suitable for the quantitative determination of these nitrosoamines and suggests a possible means of investigating their acid denitrosation.

The presence of nitro-groups in the aromatic nucleus of the nitrosoamine molecule causes a marked decrease in the velocity of the decomposition.

THE blue-violet colour produced when *N*-nitroso-*N*-ethylaniline reacts with α-naphthylamine in alcoholic hydrochloric acid was noted by Lecorché and Jovinet (*Mém. Poudres*, 1928, **23**, 147). A similar reaction takes place with many other aromatic nitrosoamines, and the object of the present investigation was to establish the mechanism of the reaction. The results obtained have shown that under certain conditions the reaction is suitable for the colorimetric determination of these compounds.

N-Nitroso-*N*-ethylaniline and its 2-nitro-, 3-nitro-, 4-nitro-, 2 : 4-dinitro-, and 2 : 4 : 6-trinitro-derivatives were selected for study. The intensity of colour produced by each of these compounds under selected conditions of test was measured with a "Spekker" photoelectric absorptiometer and determined as a function of the time of heating at 60°. The depth of colour increased with time and finally reached a maximum and almost constant value (Fig. 1), except with the trinitro-compound which gave only a faint colour after 6 hours at 60°.

The maximum colour intensities at different concentrations are shown graphically (Fig. 2). In each case a straight-line relationship was demonstrated within the normal range of the absorptiometer. Comparison of the slopes of these graphs gives a direct estimate of the relative amount of colour produced from 1 mg. of each of the nitrosoamines. The slopes are in the following ratio :

N-nitroso-*N*-ethylaniline : mononitro-derivatives : dinitro-derivatives = 1·62 : 1·28 : 1·00

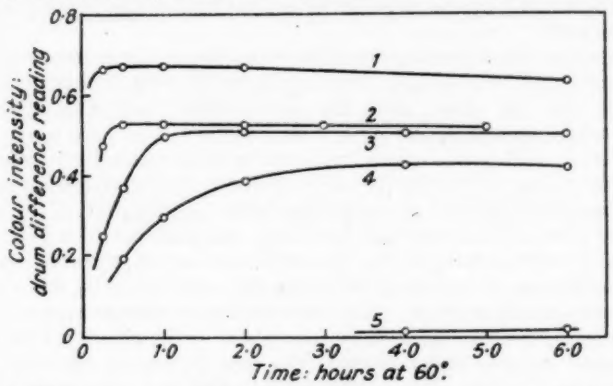
and are thus almost exactly proportional to the reciprocal molecular weights (*i.e.*, 1·60 : 1·30 : 1·00). This result suggests that the agent producing the colour is nitrous acid, which would be liberated from the nitrosoamines in just this proportion. By treatment of dilute alcoholic solutions of sodium nitrite with α-naphthylamine and alcoholic hydrochloric acid in the same way, solutions of identical tint were produced, the slope of the colour intensity–concentration curve being roughly proportional to the reciprocal of the molecular weight of sodium nitrite.

The action of nitrous acid upon an excess of α-naphthylamine would be expected to produce either 1 : 1′-diazoaminonaphthalene or 4-amino-1 : 1′-azonaphthalene. The dye obtained from the nitrosoamines had

indicator properties, being red-brown in alkaline solutions and blue-violet in acid solution, and was identified as 4-amino-1 : 1′-azonaphthalene.

FIG. 1.

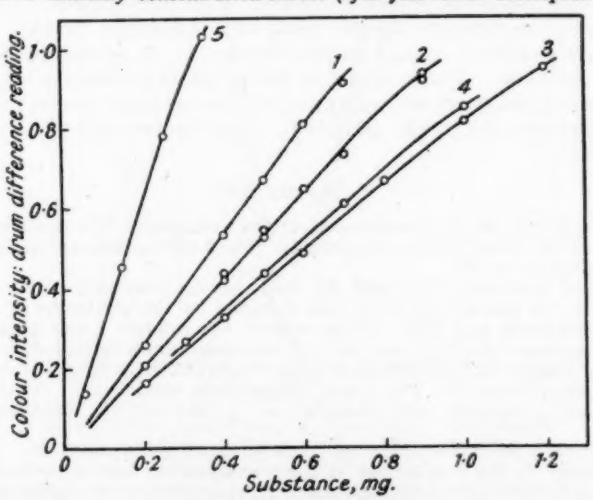
Rates of development of colour at 60° (as measured by " Spekker " absorption).



(1) N-*Nitroso*-N-*ethylaniline.*
(2) 4-*Nitro- and* 3-*nitro-derivatives.*
(3) 2-*Nitro-derivative.*
(4) 2 : 4-*Dinitro-derivative.*
(5) 2 : 4 : 6-*Trinitro-derivative.*

FIG. 2.

Colour intensity–concentration curves (after full colour development).



(1) N-*Nitroso*-N-*ethylaniline.*
(2) *Mononitro-derivatives.*
(3) 2 : 4-*Dinitro-derivative.*
(4) 4-*Amino*-1 : 1′-*azonaphthalene.*
(5) *Sodium nitrite.*

From the colour intensity–concentration curve for solutions of 4-amino-1 : 1′-azonaphthalene in N/10-alcoholic hydrochloric acid was calculated the percentage of available nitrous acid in each of the nitrosoamines which is converted into this dye (see Table).

Compound (in N/10-alcoholic hydrochloric acid).	Available nitrous acid converted into the dye (%).
Sodium nitrite	85
N-Nitroso-*N*-ethylaniline	79
2-Nitro-derivative	77
3-Nitro-derivative	77
4-Nitro-derivative	77
2 : 4-Dinitro-derivative	78

It appears that (with dilute solutions in N/10-alcoholic hydrochloric acid) about 85% of free nitrous acid is converted into the dye, whereas with the nitrosoamines a little less than 80% of the available nitrous acid is converted. This discrepancy can be partly explained by the fact that the nitrosoamines are not quantitatively converted into the free bases. Thus from absorption measurements it appears that only 96% of the 4-nitro-derivative is recoverable as 4-nitro-*N*-ethylaniline. The fate of the remaining 4% of nitrosoamine and 15% of nitrous acid has not been determined.

Neber and Rauscher (*Annalen*, 1942, **550**, 182) have shown that the Fischer–Hepp rearrangement of

N-nitrosoamines to their nuclear substituted isomers takes place in alcoholic hydrochloric acid through the intermediate formation of nitrosyl chloride. It is probable, therefore, that this is also the intermediate in the production of the colour with α-naphthylamine. It is significant that the use of sulphuric in place of hydrochloric acid reduces the intensity of the colour developed (after ½ hour at 60°) to about one quarter. However, the concentrations of nitrosoamine used in the present investigation were extremely small when compared with those used by the above workers.

Purely aliphatic nitrosoamines do not undergo this denitrosation in acid media. Thus solutions of dimethyl- and diethyl-nitrosoamine developed very little colour even after prolonged heating with α-naphthylamine and alcoholic hydrochloric acid. On the other hand, the rate of denitrosation of diphenylnitrosoamine was far greater than that of phenylethylnitrosoamine.

Since the reaction of nitrous acid with α-naphthylamine in N/10 alcoholic hydrochloric acid is very rapid, even at room temperature, the rate at which the dye is produced from the nitrosoamines is clearly a measure of the rate of their decomposition into the corresponding bases with the liberation of the nitroso-group. Assuming this denitrosation to be an electrophilic reaction involving the addition of a proton to the amino-nitrogen atom, the effect of aromatic substituents upon the rate of denitrosation is readily explained by the electronic theory. The aliphatic nitrosoamines do not react, owing to the polarisation by the nitroso-group which induces a positive charge on the amino-nitrogen atom. The introduction of the polarisable aromatic nucleus reduces this positive charge, enabling the proton addition to take place, while the introduction of electron-attracting nitro-groups into the aromatic nucleus again reduces the ease of proton addition. No doubt the marked decrease in reaction velocity which occurs when a nitro-group enters the *ortho* position is due to the introduction of a steric factor which considerably reduces the number of effective collisions of proton and nitrosoamine molecule.

The part played by ethyl alcohol in the reaction mechanism is not clear, but as the alcohol is diluted with water the reaction velocity decreases progressively until an alcohol content of about 65% w/w is reached. Further dilution causes an increase in the reaction velocity. This effect appears to be due to the change in pH of the solution which accompanies dilution, the pH being at a maximum for 65% alcohol.

The decomposition of nitrosoamines in acid media appears to be analogous to the decomposition of *N*-nitroamines under similar conditions. For example, in the presence of dilute mineral acid, the nitro-group in phenylmethylnitroamine readily splits off and migrates into the aromatic nucleus with the formation of *o*- and *p*-nitromethylanilines (Bamberger, *Ber.*, 1897, **30**, 1253). The dinitro- and trinitro-phenylmethylnitroamines are, however, far more stable.

Experimental.

N-Nitroso-*N*-ethylaniline and its 2-, 3-, and 4-nitro-derivatives were prepared in the normal manner by the treatment of hydrochloric acid solutions of the amines with sodium nitrite. The 2-nitro-nitrosoamine had m. p. 33·3—34·3°. Hempel (*J. pr. Chem.*, 1890, **41**, 167) gives m. p. 30°.

The method of Stoermer and Hoffman (*Ber.*, 1898, **31**, 2531) for the preparation of 2 : 4-dinitro-*N*-nitroso-*N*-ethylaniline gave rather poor yields. A satisfactory yield was obtained by the treatment of a solution of 2 : 4-dinitro-*N*-ethylaniline in concentrated sulphuric acid with sodium nitrite, the product being isolated by pouring the reaction mixture on crushed ice. For the removal of the last traces of unchanged dinitroamine the product was chromatographed using a 1 : 1 mixture of silica gel–celite as adsorbent and 10% of ethyl ether in light petroleum as developer (the nitrosoamine was more strongly adsorbed than the free amine under these conditions). After a final crystallisation from benzene–ligroin, small pale yellow platelets were obtained, m. p. 55·1—55·8°. Stoermer and Hoffman give 51·5—52·5°.

No record of 2 : 4 : 6-trinitro-*N*-nitroso-*N*-ethylaniline could be found in the literature. This compound was prepared by a method similar to that used for the preparation of the corresponding dinitronitrosoamine, final purification being effected by chromatography as before. After crystallisation from alcohol, pale yellow crystals were obtained, m. p. 73·0°. The *compound* gave a deep blue colour on treatment with diphenylamine in concentrated sulphuric acid. The presence of three nitro-groups and one nitroso-group was confirmed by titration of a small quantity with titanous sulphate [1 equiv. of titanous sulphate corresponded to 12·0 g. of the compound. $C_6H_2(NO_2)_3{\cdot}N(C_2H_5){\cdot}NO$ requires 11·88 g.].

4-Amino-1 : 1′-azonaphthalene was prepared by the method of Michaelis and Erdmann (*Ber.*, 1895, **28**, 2198), and had m. p. 175·5—176° (Found: C, 80·95; H, 5·13; N, 14·05; *M* (in benzene), 291. Calc. for $C_{20}H_{15}N_3$: C, 80·77; H, 5·09; N, 14·14%; *M*, 297·1).

Reagents.—Some batches of 95% alcohol or methylated spirits contained traces of impurities (possibly nitrites) which produced a small amount of colour when treated with α-naphthylamine and hydrochloric acid. In addition, certain impurities normally present in the alcohol interfere with the full colour development of the nitrosoamine under the specified conditions. All alcohol was therefore purified by distillation over lime through an efficient fractionating column (a column 4½ feet long and 2½ inches in diameter, packed with glass cuts proved satisfactory).

"AnalaR" α-Naphthylamine was recrystallised from boiling light petroleum (b. p. 40—60°). The product was dissolved in purified alcohol to give a 1% solution.

Dry hydrogen chloride was dissolved in purified alcohol to give a 2N-solution.

Rate of Development of Colour from the Nitrosoamines at 60°.—0·5 Mg. quantities of each of the nitrosoamines, dissolved in 5 ml. of purified alcohol, were placed in 100 ml. calibrated flasks. 80 Ml. of purified alcohol, 5 ml. of hydrochloric acid reagent, and 5 ml. of 1% α-naphthylamine solution were added to each. The flasks were kept in a water-bath at 60° ± 2° for various periods, after which they were transferred to a bath at 20° for 1 hour. A blank test with the reagents alone was included.

The solutions were then made up to 100 ml. and their extinctions (*i.e.*, difference in drum reading between blank and sample solutions) measured with the "Spekker" absorptiometer, using 1 cm. cells, a water-to-water setting of 1·00, and Ilford yellow-green filters No. 605.

The results obtained for the six nitrosoamines are given in a graph (Fig. 1) showing colour intensity (in terms of "Spekker" drum difference reading) plotted against time of colour development at 60°.

Construction of Colour Intensity–Concentration Curves.—The procedure described in the previous paragraph was

applied to various quantities of each nitrosoamine, adopting the appropriate times for maximum colour development, as follows :

N-Nitroso-*N*-ethylaniline	30 minutes.		
4-Nitro-derivative	30 ,,	2-Nitro-derivative	3 hours.
3-Nitro-derivative	30 ,,	2 : 4-Dinitro-derivative	4 ,,

Curves were similarly obtained for sodium nitrite and 4-amino-1 : 1′-azonaphthalene (except that no heating at 60° was necessary for the development of the colour), using the same quantities of reagents. All these curves are shown in Fig. 2.

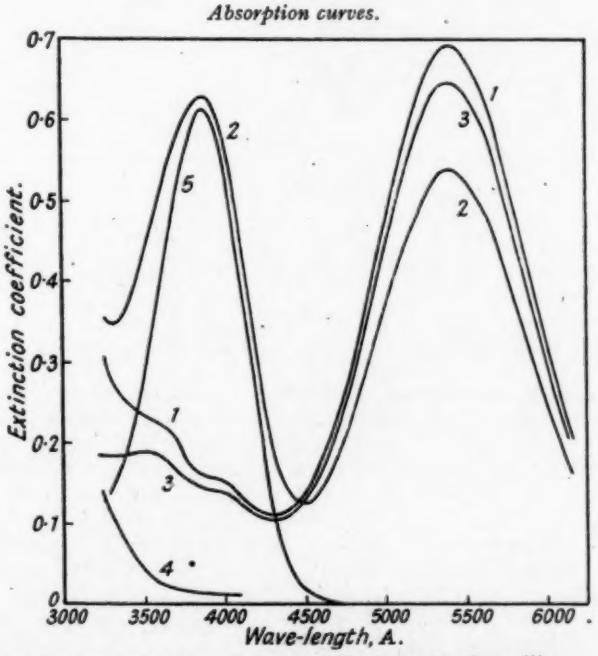
Effect of Variation of the Concentration of the Reagents.—In order to select the optimum conditions for the colour reaction, experiments were carried out in which the concentrations of hydrochloric acid and α-naphthylamine were varied. Concentrations lower than those selected failed to produce a full colour development in the times chosen.

Stability of the Coloured Solutions.—The coloured solutions resulting from the reactions studied were quite stable when stored in the dark. No significant change was detected during one week, but on prolonged storage a slight fading of the colour was noticed.

Constitution of the Dye.—(*a*) After treating 0·2 g. of sodium nitrite and 0·3 g. of *N*-nitroso-*N*-ethylaniline severally with α-naphthylamine under the selected conditions, small quantities of the resulting dye (as the free base) were isolated and identified by m. p. in admixture with 4-amino-1 : 1′-azonaphthalene. *N*-Ethylaniline was isolated from the products of the second reaction.

FIG. 3.

Absorption curves.



(1) *Solution derived from* 0·5 *mg. of* N-*nitroso*-N-*ethylaniline.*
(2) *Solution derived from* 0·5 *mg. of the* 4-*nitro-derivative.*
(3) *Solution of* 4-*amino*-1 : 1′-*azonaphthalene in* N/10-*alcoholic* HCl.
(4) 0·05 *G. of* α-*naphthylamine in* 100 *ml. of* N/10-*alcoholic* HCl.
(5) 0·5 *Mg. of* 4-*nitro*-N-*ethylaniline in* 100 *ml. of* 95% *alcohol.*

(*b*) Absorption curves were obtained over the range 3250—6500 A. for the following solutions (see Fig. 3) :

(i) That obtained by treating 0·5 mg. of *N*-nitroso-*N*-ethylaniline in alcoholic hydrochloric acid with α-naphthylamine under the selected conditions.

(ii) That obtained by the similar treatment of 0·5 mg. of the 4-nitro-derivative.

(iii) 4-Amino-1 : 1′-azonaphthalene in 0·1N-alcoholic hydrochloric acid.

(iv) A blank solution containing 0·05 g. of α-naphthylamine in 100 ml. of 0·1N-alcoholic hydrochloric acid.

(v) 0·5 Mg. of 4-nitro-*N*-ethylaniline in 100 ml. of 95% alcohol.

The solution of the hydrochloride of 4-amino-1 : 1′-azonaphthalene shows a maximum at 5400—5420 A. and two plateaux at 3250—3500 A. and 3750—4000 A. Both solutions (i) and (ii) show the maximum at 5400—5420 A. and the solution derived from the *N*-nitroso-*N*-ethylaniline (i) shows the two plateaux (although modified by the rise in absorption from 4000 to 3250 A. caused by the presence of the α-naphthylamine). In solution (ii) the plateaux are completely obscured by the maximum which this solution shows at 3850—3870 A. This corresponds to the maximum shown by the solution of 4-nitro-*N*-ethylaniline in 95% alcohol. The relative heights of the latter maxima (after correction for the absorption shown by the dye at this wave-length) indicate that 96% of the 4-nitronitrosoamine has been converted into 4-nitro-*N*-ethylaniline.

The absorption curves were obtained with a Beckman Quartz Photoelectric Spectrophotometer, using a tungsten filament lamp as light source and slit widths such that the sensitivity control was set at three turns from its clockwise limit.

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159. *The Ethylmercury Phosphates.*

By A. D. Ainley, L. A. Elson, and W. A. Sexton.

A study of the reaction between tetraethyl-lead, mercuric oxide, and phosphoric acid has led to the preparation and characterisation of the three ethylmercury phosphates. Bisethylmercury phosphate gives addition compounds with diethyl-lead phosphate and with anthraquinone-1-sulphonic acid.

The only mention of an ethylmercury phosphate in the literature is by Dünhaupt (*J. pr. Chem.*, 1854, **61**, 399) who, by treatment of an alcoholic solution of ethylmercury chloride with silver phosphate isolated the phosphate as a crystalline mass, very soluble in water. No melting point or analysis was given. As silver phosphate is usually regarded as being Ag_3PO_4 (Mellor, "A Comprehensive Treatise on Inorganic and Theoretical Chemistry," Longmans & Co., Vol. III, p. 485), it would appear that the product isolated by Dünhaupt was trisethylmercury phosphate $(C_2H_5Hg)_3PO_4$.

The three possible ethylmercury phosphates have now been prepared and characterised, and it has been shown that the product prepared by Dünhaupt's method is not pure but consists mainly of the *trisethylmercury phosphate* together with some of the difficulty separable *bis-salt* $(C_2H_5Hg)_2HPO_4$.

For the preparation of the three ethylmercury phosphates in pure form use was made of the method of preparation of ethylmercury salts from tetraethyl-lead described in B.P. 331,494. It is well known that the mobility of alkyl or aryl groups in compounds of the type PbR_4 in reaction with metallic halides, *e.g.*, mercury, bismuth, thallium, arsenic, etc., is a general property of such groups attached to electropositive elements (Calingaert, *Chem. Rev.*, 1925, **2**, 43; Friend, "Text Book of Inorganic Chemistry," Griffin & Co., Vol. XI, Part I, p. 340). By treating tetraethyl-lead with mercuric oxide and the equivalent quantities of phosphoric acid required by the equations (*b*), (*c*), and (*d*) it should be possible to prepare all three ethylmercury phosphates, and this has been done.

(*a*) $HgO + 2H_3PO_4 + PbEt_4 \longrightarrow Et_2Hg + Et_2Pb(H_2PO_4)_2 + H_2O.$
(*b*) $2HgO + 4H_3PO_4 + PbEt_4 \longrightarrow 2EtHgH_2PO_4 + Et_2Pb(H_2PO_4)_2 + 2H_2O.$
(*c*) $2HgO + 2H_3PO_4 + PbEt_4 \longrightarrow (EtHg)_2HPO_4 + Et_2PbHPO_4 + 2H_2O.$
(*d*) $6HgO + 4H_3PO_4 + 3PbEt_4 \longrightarrow 2(EtHg)_3PO_4 + (Et_2Pb)_3(PO_4)_2 + 6H_2O.$
(*e*) $HgO + 2H_3PO_4 + PbEt_4 \longrightarrow EtHgH_2PO_4 + Et_2PbH_2PO_4 + H_2O.$

It was not possible to isolate *ethylmercury phosphate* by utilisation of only one ethyl group of tetraethyl-lead according to equation (*e*), the reaction proceeding further with ultimate formation of diethylmercury and diethyl-lead phosphate [equation (*a*)], thus affording another example of the alkylating action of triethyl-lead salts. In the case of bisethylmercury phosphate the lead compound as formed is already of type R_2PbX_2 and would thus not show the tendency to react further with the mercuric oxide and phosphoric acid. No diethylmercury was formed during this reaction and bisethylmercury phosphate is the most readily obtainable and easily characterised of the ethylmercury phosphates. It has been found, however, that when the reaction is carried out in alcohol according to equation (*c*) only half the product can be isolated by filtration and evaporation of the alcohol, although the mercurial phosphate is readily soluble in alcohol. The remainder is present as an alcohol-insoluble complex compound corresponding approximately to the composition $(EtHg)_2HPO_4,2Et_2PbHPO_4$. This complex, although stable to boiling alcohol, is decomposed quantitatively by cold water into an insoluble lead compound and bisethylmercury phosphate. No complex-salt formation has been observed in reactions (*b*) and (*d*) since trisethylmercury phosphate can be completely extracted by means of alcohol. The reaction (*d*), however, proceeds much more slowly than (*b*) and (*c*).

The three ethylmercury phosphates are crystalline compounds of characteristic m. p.'s which are depressed on admixture. Bisethylmercury phosphate reacts with phosphoric acid to give the mono-salt $EtHgH_2PO_4$. This is evidently a balanced reaction, for recrystallisation of the latter from alcohol always gave small quantities of the bisethylmercury salt.

In preparing a number of ethylmercury salts for fungicidal evaluation we had occasion to study the reaction between the bis-salt and sodium anthraquinone-1-sulphonate. This gave rise to a crystalline *compound* containing an amount of mercury corresponding to the composition $C_{14}H_7O_2SO_3HgEt,2(EtHg)_2HPO_4$. A complete investigation of the constitution of this compound has not been made, but the presence of phosphate was detected qualitatively and it was ascertained by rough titration with aqueous sodium chloride that only part of the ethylmercury was immediately precipitable as the insoluble chloride, the remainder being more firmly bound. Attempts to prepare an addition compound of bisethylmercury phosphate with anthraquinone itself were unsuccessful.

Experimental.

Ethylmercury Phosphate, $EtHgH_2PO_4$.—Bisethylmercury phosphate (5 g.) was dissolved in hot alcohol containing 90% phosphoric acid (2 g.), and the solution allowed to cool; crystals of *ethylmercury phosphate* separated, m. p. after recrystallisation from alcohol 115° (Found: Hg, 61·2. $C_2H_7O_4PHg$ requires Hg, 61·1%).

With the proportions of reagents required by equation (*a*), under the conditions used for making bisethylmercury phosphate (see below), the insoluble organic lead compound contained no mercury and it was not possible to isolate a pure ethylmercury phosphate from the reaction mixture. The alcohol was removed by distillation, and addition of water precipitated a heavy oil. That this contained diethylmercury was demonstrated by its conversion by means of warm concentrated hydrochloric acid into ethylmercury chloride, identified by mixed m. p. with authentic material.

Mercuric oxide (21·6 g.) was suspended in absolute ethyl alcohol (100 c.c.) and a mixture of 90% phosphoric acid (22 g.) and absolute ethyl alcohol (50 c.c.) added to the stirred suspension. After 5 minutes' stirring, tetraethyl-lead (16·2 g.) was added dropwise during 20 minutes to the stirred mixture and the stirring was continued for 30 minutes, during which the greater part of the mercuric oxide disappeared with simultaneous formation of a heavy white solid. The temperature of the reaction mixture rose to 40° during the addition and the reaction was completed by heating under reflux for 30 minutes, *i.e.*, until the last traces of mercuric oxide had disappeared. The hot reaction mixture was filtered, the white insoluble residue washed with hot alcohol and the combined filtrate and washings evaporated to small bulk. Crystallisation of the product (24·2 g.) from a small volume of ethyl alcohol gave ethylmercury phosphate as small, colourless prisms, m. p. and mixed m. p. with material prepared as above 115°. Crystallisation of a pure sample of ethylmercury phosphate from ethyl alcohol gave initially a small amount of large shining plates of bisethylmercury hydrogen phosphate, m. p. and mixed m. p. with an authentic specimen (prepared as below) 175—176°, followed by the main crop of the monoethylmercury derivative.

Bisethylmercury Phosphate, $(EtHg)_2HPO_4$.—90% Phosphoric acid (8·5 g.) was dissolved in alcohol (100 c.c.), and mercuric oxide (16·5 g.) added. Tetraethyl-lead (12·4 g.) was added dropwise during 10 minutes to the stirred mixture, after which the reaction was completed by boiling until the yellow colour of mercuric oxide disappeared (½ hr.). The hot reaction mixture was filtered and the insoluble material washed with hot alcohol. Evaporation of the filtrate and washings afforded crystals of *bisethylmercury phosphate*, m. p. after recrystallisation from alcohol 176° (Found: Hg, 72·4. $C_4H_{11}O_4PHg_2$ requires Hg, 72·2%). [Since our work was carried out, Rumpf (*A.*, 1945, II, 379) has given m. p. 176° for this compound prepared from the hydroxide and phosphoric acid.] The residue insoluble in alcohol could not be purified by crystallisation and the mean analyses of the product from several experiments gave Hg, 32; Pb, 30% approx. The double compound formulated above requires Hg, 31·5; Pb, 32·5%. Extraction of the residue with water removed all the mercury, which was recovered from the aqueous extract by evaporation in the form of bisethylmercury phosphate, m. p. 174—176° undepressed on admixture with the original material obtained from alcohol.

Trisethylmercury Phosphate, $(EtHg)_3PO_4$.—Mercuric oxide (43·3 g.), 90% phosphoric acid (14·5 g.), and tetraethyl-lead (20 c.c.) in hot alcohol (150 c.c.) were boiled as described in the preceding paragraph, 4 hours' boiling being necessary to ensure disappearance of the yellow oxide. The residue after filtration contained no mercury, and the filtrate was evaporated to dryness, yielding *trisethylmercury phosphate*. Purified by repeated crystallisation from alcohol–ethyl acetate, it formed colourless prisms which softened at 110° and melted at 145° (Found: Hg, 76·1. $C_6H_{15}O_4PHg_3$ requires Hg, 76·7%).

Reaction of Silver Phosphate and Ethylmercury Bromide.—To an aqueous solution of silver nitrate (25 g.) was added a saturated solution of disodium hydrogen phosphate until there was no further precipitate of silver phosphate. The precipitate was washed with alcohol, suspended in alcohol, and an equivalent quantity of ethylmercury bromide added. After digestion with occasional shaking and warming for 2 days, the reaction mixture was filtered and the filtrate evaporated to dryness. The product resisted purification by crystallisation from alcohol or benzene and its m. p. was indefinite. A small quantity of bisethylmercury phosphate (0·5 g.) was eventually obtained by careful manipulation, but the main bulk of material melted over the range 115—135° (cf. trisethylmercury phosphate, m. p. 145° with previous softening).

Ethylmercury Anthraquinone-1-sulphonate.—Sodium anthraquinone-1-sulphonate (6·2 g.) in hot water (140 c.c.) was added to a solution of bisethylmercury phosphate (11 g.) in water (70 c.c.). A small amount of flocculent precipitate was removed, and the solution allowed to cool. The crystals which separated were removed and the filtrate evaporated to dryness. Recrystallisation from water or alcohol gave clusters of pale yellow needles, m. p. 213—214° (decomp.) (Found: Hg, 62·3. $C_{24}H_{24}O_{13}SP_2Hg_5$ requires Hg, 61·6%). The molybdate test was positive for phosphate, and the *compound* gave no precipitate with sodium hydroxide.

The above compound (5 g.) was dissolved in warm water (200 c.c.) and 10% sodium chloride gradually added. After the addition of 5 c.c. (corresponding to three-fifths of the ethylmercury present) there was no further immediate precipitate of ethylmercury chloride. The amount separated by filtration (2·18 g.) was approximately equivalent to three ethylmercury radicals as ethylmercury chloride (theory, 2·4 g.). Addition of hydrochloric acid to the filtrate gave an immediate precipitate of ethylmercury chloride.

Bisethylmercury Phosphate and Anthraquinone.—Reaction between these two substances was attempted in boiling alcohol for 20 hours, and in β-ethoxyethyl alcohol or anisole overnight on the steam-bath. No compound formation was observed.

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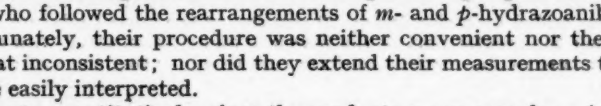
160. *The Kinetics of Some Benzidine Rearrangements, and a Note on the Mechanism of Aromatic Substitution.*

By M. J. S. DEWAR.

Hydrazobenzenes can be estimated in presence of their rearrangement products by titration with Bindschedler's green. In this way the rates of rearrangement at 0° and 22·7° of hydrazobenzene, *o*-hydrazoanisole, m-*hydrazoanisole*, and *p*-hydrazotoluene have been determined, and activation energies calculated. The reactions were unimolecular. Only the salts appeared to rearrange. The results support the new mechanism recently put forward (Dewar, *Nature*, 1945, **156**, 784; this vol., p. 406) and are at variance with other electronic mechanisms that have been suggested. The theory of π-electron sharing is extended to cover aromatic substitution; certain anomalies in the older theories may thus be avoided.

IT was suggested recently (Dewar, *loc. cit.*) that various rearrangements of the benzidine type could be readily interpreted in terms of a new concept—that of a bond formed by sharing of π-electrons between aromatic systems and not by localised electron-pairs shared between definite atoms. This theory also explains various other reactions of aromatic and olefinic compounds, and it was therefore desirable that definite evidence for it should be sought; the present paper describes experiments carried out with that object. These have centred on the benzidine rearrangement itself, since, in spite of its inherent interest and importance, it has been little investigated in recent years. The rates of several such rearrangements have now been determined and the results do indeed appear to support the new theory.

The only kinetic investigation of benzidine rearrangements that has been previously reported was that of Biilmann and Blom (*J.*, 1924, **125**, 1719), who followed the rearrangements of *m*- and *p*-hydrazoaniline by an ingenious potentiometric method. Unfortunately, their procedure was neither convenient nor theoretically satisfactory, and their results were somewhat inconsistent; nor did they extend their measurements to simpler cases where the data might have been more easily interpreted.

It is difficult to follow these rearrangements quantitatively, since the products are so complex: in addition to derivatives of diphenyl and diphenylamine, azo-compounds and amines are always formed by a disproportionation (see Ingold and Kidd, *J.*, 1933, 984). It is not easy to estimate hydrazobenzene in the presence of these substances, and the authors cited found iodine titration and estimation with Fehling's solution inadequate for the purpose. It has now been discovered that hydrazobenzene is instantaneously and quantitatively oxidised to azobenzene by the redox indicator, Bindschedler's green,  , and can be titrated with the dye even in 0·001N-solution. The dye acts as its own indicator and the products of the rearrangements do not interfere with the estimation. In this way the rearrangements of hydrazobenzene, *o*-hydrazoanisole and m-*hydrazoanisole*, and also the semidine rearrangement of *p*-hydrazotoluene, have been investigated at 0° and 22·7°; in the last case the velocity constants are less reliable, since the semidine was attacked by the oxidising agent.

Experimental.

Materials.—Hydrazobenzene, *o*-hydrazoanisole, and *p*-hydrazotoluene were prepared by standard methods and crystallised several times from alcohol; their properties agreed with those given in the literature. No details for the preparation of Bindschedler's green were available; the following procedure was satisfactory. Zinc dust was added to a solution of *p*-nitrosodimethylaniline hydrochloride (18·7 g.; 0·1 g.-mol.) in hydrochloric acid (200 c.c. of 20%), the temperature being kept below 30°. When the solution was no longer yellow, the zinc was filtered off and washed with a little water. The combined filtrates were mixed with a solution of dimethylaniline (12·1 g., 0·1 g.-mol.) in hydrochloric acid (100 c.c. of 20%), cooled to 0°, and a saturated solution of potassium dichromate (19·2 g.) in water added with stirring. After 20 minutes the zincichloride of the dye was collected, washed with ice-water, alcohol, and ether, and dried in an oven. This material (28—30 g.) was pure enough for the present purpose (98·6% by titration with titanous sulphate).

m-*Hydrazoanisole.*—A mixture of *m*-nitroanisole (62·5 g.), methanol (250 c.c.), sodium hydroxide (70 g.), and water (50 c.c.) was heated under reflux and stirred mechanically while zinc dust (135 g.) was gradually added, and heating was then continued till the solution was colourless (2 hours). When it was cold, chloroform (750 c.c.) was added, the zinc filtered off and washed with chloroform, and the combined chloroform extracts evaporated under reduced pressure. The resulting m-*hydrazoanisole* crystallised on scratching with light petroleum and was then recrystallised from carbon tetrachloride, forming large, pale yellow, rectangular tablets, m. p. 59—60° [Found: C, 68·5, 68·6; H, 6·5, 6·8; N, 11·3; OMe, 25·2. $C_{12}H_{10}N_2(O\cdot CH_3)_2$ requires C, 68·8; H, 6·6; N, 11·5; OMe, 25·4%).

m-*Azoanisole.*—Prepared from the hydrazine by iodine oxidation, m-*azoanisole* crystallised from methanol in large, orange-brown plates, m. p. 78—79° (Found: C, 69·0; H, 5·9. $C_{14}H_{14}O_2N_2$ requires C, 69·4; H, 5·8%).

Procedure.—Equal volumes of hydrazobenzene solution (*ca.* 0·02N) and catalyst solution (0·2N) were mixed in an inert atmosphere, and at intervals portions were removed for analysis. In the more rapid reactions a batch method was necessary. The estimations of hydrazobenzene and its methoxyl derivatives were effected by addition to excess of standard Bindschedler's green solution and back-titration with titanous sulphate (both *ca.* 0·01N). This method was not suitable for *p*-hydrazotoluene, since the semidine formed by rearrangement was attacked by the dye; consistent results were, however, obtained by direct titration with the dye, provided that this was carried out rapidly and that the concentration of semidine was not too great. The dye solutions were somewhat unstable; they were standardised at half-hour intervals and always used within four hours of preparation. During rearrangement, the catalyst is removed by salt formation with the basic products; with the concentrations used the resulting decrease in rate was not appreciable.

Table I.

o-Hydrazoanisole; 0·1M-$H\cdot CO_2H$; 0·1M-$H\cdot CO_2Na$; 80% EtOH; 22·7°.

t, mins.	*x*, obs.	*x*, calc.	$10^4\times$ 0·4343*k*.	*x*, obs.	*x*, calc.	$10^4\times$ 0·4343*k*.	*t*, mins.	*x*, obs.	*x*, calc.	$10^4\times$ 0·4343*k*.	*x*, obs.	*x*, calc.	$10^4\times$ 0·4343*k*.
0	24·4	—	—	21·1	—	—	28	15·4	15·3	1·19	$13·0_5$	13·2	1·24
8	21·3	21·3	1·23	$18·4_5$	18·5	1·21	32	$14·4_5$	14·3	1·18	12·4	12·4	1·20
12	$19·9_5$	20·0	1·21	$17·2_5$	17·3	1·22	36	13·6	13·4	1·18	$11·5_5$	11·6	1·21
16	18·7	18·7	1·20	16·1	16·2	1·22	40	12·6	12·5	1·20	$10·7_5$	10·8	1·22
20	17·4	17·5	1·22	15·0	15·1	1·23	44	$11·8_5$	11·7	1·19	10·0	10·1	1·23
24	16·4	16·4	1·20	$14·1_5$	$14·1_5$	1·21	48	11·1	11·0	1·19	—	—	—
							52	$10·3_5$	10·2	1·18	—	—	—

Table II.

	Catalyst.	Solvent.	10^5k. (0°).	10^4k (22·7°).	Frequency factor.	*E*, cals.
Hydrazobenzene	HCl	EtOH	271 ±3	322 ±11·5	$2·8\times10^{11}$	17,610
Hydrazobenzene	HCl	75% EtOH	3·55 ±0·07	4·05 ±0·05	$2·1\times10^{9}$	17,320
o-Hydrazoanisole	$H\cdot CO_2H$–$H\cdot CO_2Na$	80% EtOH	4·57 ±0·04	2·77 ±0·03	$7·2\times10^{5}$	12,820
m-Hydrazoanisole ...	HCl	75% EtOH	6·82 ±0·03	10·85 ±0·16	$3·1\times10^{11}$	19,680
p-Hydrazotoluene ...	$CH_2Cl\cdot CO_2H$–$CH_2Cl\cdot CO_2Na$	75% EtOH	4·10 ±0·14	2·20 ±0·10	$1·3\times10^{5}$	11,950
Hydrazobenzene	$CCl_3\cdot CO_2H$	75% EtOH	—	0·788 ±0·019	—	—

Results.—Preliminary experiments established the following points. The rearrangements were unimolecular (cf. Bülmann and Blom, *loc. cit.*). Rearrangement in alcoholic hydrogen chloride at room temperature was extraordinarily fast; that of *o*-hydrazoanisole was virtually instantaneous. On the other hand, hydrazobenzene was little affected by 0·1N-alcoholic trichloroacetic acid (*ca.* 3% conversion in 6 hours at 22·7°). In anhydrous formic acid rearrangement was extremely rapid, in glacial acetic acid very slow. Azo-compounds were formed in all cases as by-products (cf. Ingold and Kidd, *loc. cit.*).

Accurate measurements of rate were carried out at 0° in a bath of melting ice and at 22·7° ± 0·02° in a thermostat. In Table I two typical experiments are given in full to illustrate the consistency and reproducibility of the results. All the calculated values of x (the titre at time t) were derived from the same mean unimolecular rate constant ($2{\cdot}77 \times 10^{-4}$). In Table II are given mean unimolecular rate constants and mean deviations, together with activation energies and frequency factors calculated from them. Unfortunately, no suitable thermostat was available for further measurements at a higher temperature, but it is thought unlikely that the activation energies are in error by as much as 400 cals.

Discussion.

The rearrangement of hydrazobenzene, when catalysed by hydrogen chloride, is much faster in alcohol than in aqueous alcohol, but with trichloroacetic acid as catalyst the reverse is true. The ratio of the rates in alcohol is very great. These results suggest strongly that rapid and reversible salt formation precedes rearrangement, and that the reaction therefore exhibits specific catalysis by oxonium ions. The rate depends on the concentration of salt present in equilibrium. Trichloroacetic acid is a weak acid in absolute alcohol; therefore in alcoholic trichloroacetic acid little of the hydrazobenzene is present as its salt, and rearrangement is slower than in aqueous alcohol where the acid is more highly dissociated. With hydrochloric acid as catalyst, on the other hand, the rate is greater in alcohol, since hydrochloric acid is a strong acid in both solvents and the ethyloxonium cation is more strongly acidic than oxonium. In this case salt formation is more complete in the absence of water.

The activation energies of the hydrochloric acid-catalysed rearrangements in alcohol and in aqueous alcohol were the same within the limits of experimental error, the difference in rates being due mainly to a change in the frequency factor; this is easily understandable if the rate-determining step is not the formation but the rearrangement of the salt. It was fortunate that the activation energies were apparently independent of the conditions used. The range of velocities observed was much too great for study under any one set of conditions.

It had appeared extremely unlikely for other reasons that salt formation could be the rate-determining step in these rearrangements. Hydrazobenzene and its derivatives are appreciably basic, forming salts in aprotic solvents (Orelkin, Rysskaltschuk, and Aisikowitsch, *J. Gen. Chem. U.S.S.R.*, 1931, **1**, 696). Analogy with aniline, diphenylamine, and phenylhydrazine, where the introduction of each phenyl group raises the basic pK by about 4 units, suggests that hydrazobenzene should have a pK of *ca.* 14. Slow proton transfer to a nitrogen atom with this order of basicity is extremely improbable.

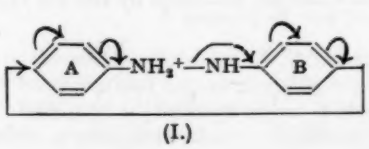
If we correct the frequency factors for the benzidine rearrangements in Table II for the varying concentrations of hydrazobenzene salt present under the operative conditions, assuming that acids have similar dissociation constants in water and in aqueous alcohol, the corrected frequency factors vary little and the variations may well be due to small differences in basicity. The entropies of activation of all these rearrangements must then be similar, and the activation energies are a true measure of the potential energy of activation. The order of decreasing ease of rearrangement is then *o*-hydrazoanisole $\gg$ hydrazobenzene $>$ *m*-hydrazoanisole. The corrected frequency factors were, moreover, normal for unimolecular reactions.

The semidine rearrangement of *p*-hydrazotoluene was abnormal, however, being evidently a "slow" reaction; the low frequency factor cannot be ascribed to a basicity effect, since hydrazotoluene must be at least as strong a base as hydrazobenzene. Here the entropy of activation must be abnormally small.

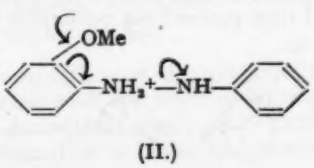
The mechanism proposed by Ingold and Kidd (*loc. cit.*; see Hughes and Ingold, *J.*, 1941, 691) differs mainly from that of Robinson (*J.*, 1941, 220) in supposing that salt-formation accompanies rearrangement. As we have seen, the evidence does not support this idea; salt formation appears to precede rearrangement.

The mechanism proposed by Robinson involves the electronic processes (I). The detailed theory involves a concept of electronic oscillations, which has been criticised, but an equivalent quantum-mechanical interpretation can be given. Hughes and Ingold also objected to this mechanism on the grounds that it requires electrons to recede from a positive centre. Certainly such a displacement could only be possible if appreciable bonding between the *p*-positions preceded fission of the N–N bond. In the transition state for such a process, however, the rings could not approach much closer than 4 A.; even in molecular complexes the interannular distance is 3·5 A. (Powell, Huse, and Cooke, *J.*, 1943, 153). It is difficult to believe that a C–C link 4 A. long and distorted at both ends could have appreciable strength, and the N–N bond would have been stretched out of existence before the carbon atoms approached within that distance.

The present work provides definite evidence against such bonding. Since it would involve anionoid attack by the *p*-position of ring B on the *p*-position of ring A, it should be facilitated by methoxyl in the position *meta* to nitrogen in ring B. A *m*-methoxyl in ring A should have little influence, its electromeric effect not being



(I.)



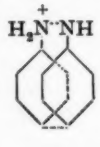
(II.)

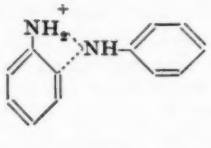
called into play. Therefore this theory would require *m*-hydrazoanisole to be rearranged much more readily than hydrazobenzene. On the other hand, *m*-methoxyl is a cationoid group as shown by its effect on the dissociation constants of acids and bases and on the rates of various reactions; therefore in *o*-hydrazoanisole the methoxyls should deactivate both rings, and rearrangement should be less facile than that of hydrazobenzene. The order of rates so predicted is diametrically opposite to that observed.

Hammick and Mason (this vol., p. 638) have recently proposed an ingenious modification of Robinson's theory which avoids its stereochemical difficulties; they suppose that ring A in the Robinson mechanism reacts in a buckled quinonoid form which allows the *p*-positions to approach within bonding distance before the N–N bond is broken. Unfortunately, this theory demands the complete destruction of the resonance of ring A in the transition state and the activation energies here reported are far too low for this to be possible. Moreover, these authors require that the semidine and other related intramolecular rearrangements should have a different and unspecified mechanism.

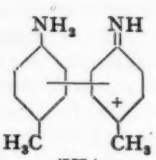
The evidence suggests rather strongly that the rate-determining step is fission of the N–N bond; this will be facilitated by methoxyl in the *o*-positions, and diminished by methoxyl in the *m*-positions, by the mechanism (II). But since the rearrangements are intramolecular (cf. Ingold and Kidd, *loc. cit.*), some bond must hold the halves of the molecule together after the N–N link has parted and before the C–C bond has formed; such a bond would moreover have to be little affected by the orientation of substituents. If so, the theory of π-electron sharing receives strong support, for it requires an intermediate phase in the reaction where the rings are held together in just this manner.

Two further pieces of evidence may be cited. The semidine rearrangement of *p*-hydrazotoluene is a " slow " reaction and must therefore have an abnormally low entropy of activation. Now the Ingold–Kidd and the Robinson theory require transition states of the types (III) and (IV) in the benzidine and the semidine rearrangement, and we should expect the latter to be not less rigid than the former; the low entropy of activation is therefore not easily explained. But the present theory requires a transition state of the type (V) for the


(III.)


(IV.)

(V.)

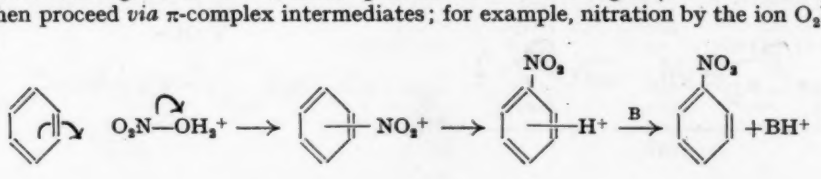

(VI.)

conversion of *p*-hydrazotoluene into the intermediate π-complex (VI); in (V) the methyl groups should mutually interfere and their rotation should be hindered. Since the entropy of free rotation of a group is large (~10 cals./°c.), the low entropy of activation is easy to understand.

Secondly, the salts formed by hydrazobenzenes in aprotic solvents, which have already been mentioned, have properties which are difficult to explain on current theory; they have intense colours, quite unlike those of the rearrangement products, and on hydrolysis they give mainly those products with only a little of the unchanged parent base. This is strange, because the rearrangements of the salts in aqueous solution are by no means instantaneous, if the present work has been rightly interpreted. If, however, these salts are actually equilibrium mixtures of the salt of the parent hydrazobenzene and of all the π-complexes formed from it by rearrangement, their properties are easily intelligible. Normally such π-complexes react further, but in the absence of adequate proton acceptors they may well be stable; on hydrolysis a mixture of the products of further reaction is obtained. Incidentally the evidence suggests that, as would be expected, more diphenyline than usual is then formed; normally the π-complex has not time to reach equilibrium (and therefore the benzidine is favoured). The colour of the salts finds analogy in the colour of solutions of aromatic hydrocarbons in anhydrous hydrogen fluoride; this has already (Dewar, *loc. cit.*) been ascribed to π-complex formation.

The Mechanism of Aromatic Substution.

The present results raise an interesting point, *viz.*, the effect that a *m*-methoxyl group has on the rate of ordinary cationoid substitution of aromatic compounds. According to current electronic theory its effect should be cationoid and it should therefore diminish the rate; this is because methoxyl has opposed inductive and electromeric effects, and in the *m*-position only the inductive effect is operative. It is well known to organic chemists, however, that a *m*-methoxyl group actually facilitates substitution; for instance, veratrole, unlike anisole, is rapidly nitrated by cold dilute nitric acid (Cardwell and Robinson, *J.*, 1915, **107**, 256), and guaiacol reacts more easily than phenol with *N*-chloromethylphthalimide (D.R.P. 442,774; " Friedländer," **15**, 1700). This anomaly can be explained if the anionoid reactivity of the nucleus in substitution is due to its π-electrons, which are analogous to the unshared pair in tervalent nitrogen (cf. the former paper). Such reactions would then proceed *via* π-complex intermediates; for example, nitration by the ion $O_2N{\cdot}OH_2^+$ might be represented as



The complexity of the kinetics of some such reactions may be due to a possible reversibility of the first step; in any case, further investigation, particularly of *o*-disubstituted benzene derivatives, would be of interest.

Current theory does not well explain why aniline and phenol couple exclusively *para* but nitrate, chlorinate, etc., *ortho* and *para*. In the previous paper it was argued that the ability of a positive ion to form a π-complex should vary inversely as its stability, and that the intermolecular character of the aminoazobenzene rearrangement could be ascribed to the stability of the benzenediazonium cation. The same argument then leads us to suppose that aromatic substitution should occur by two distinct mechanisms: a single-step mechanism of classical type when the attack is by stable cations (*e.g.*, diazonium salts), and a two-step mechanism involving a π-complex intermediate when attack is by an unstable cation or potential cation (*e.g.*, NO_2^+, Br^+). If so aromatic substitution is, like aliphatic substitution, a dual process.

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161. *A Convenient Method of Preparation of Certain Primary Amines.*

By R. BROWN and W. E. JONES.

Various primary amines, uncontaminated by the corresponding secondary and tertiary compounds, are readily obtained by condensation of *O*-methylhydroxylamine (1 mol.) with 2 mols. of alkylmagnesium chlorides or preferably bromides, but not with iodides. The yields vary from 40 to 90%. The reaction is also applicable to aliphatic dibromides; *e.g.*, cadaverine is obtainable in 68% yield from pentamethylene bromide.

AN investigation requiring considerable quantities of *tert.*-butylamine led to an examination of its preparation on a moderately large scale. Van Erp (*Rec. Trav. chim.*, 1895, **14**, 16) and Brander (*ibid.*, 1918, **37**, 67) prepared it respectively by the Hofmann degradation of pivalic amide and by heating *tert.*-butyl chloride with ammonia, but in both cases the yields were extremely small. Coleman and Yager (*J. Amer. Chem. Soc.*, 1929, **51**, 567) obtained it in 60% yield by condensation of *tert.*-butylmagnesium chloride with chloroamine, but the instability of the latter rendered this method unsuitable for our purpose. Sheverdina and Kocheshkov (*J. Gen. Chem. Russia*, 1938, **8**, 1825), however, overcame this difficulty by replacing the chloroamine by the stable *O*-methylhydroxylamine, two mols. of Grignard compound being required.

$$2RMgCl + MeO{\cdot}NH_2 = RNH{\cdot}MgCl + RH + MeOMgCl$$

The experiments of Sheverdina and Kocheshkov (*loc. cit.*) were carried out on a very small scale (0·03 molar) and at such great dilution as to make larger-scale preparation impracticable, but suitable modifications have permitted an increase to 3-molar scale, the yield being 70% calculated on *O*-methylhydroxylamine.

A number of other halides have also been examined under the same conditions, the results being shown in the Table, together with comparative yields obtained by Sheverdina and Kocheshkov (*loc. cit.*) and by Coleman *et al.* (*loc. cit.* and *J. Amer. Chem. Soc.*, 1928, **50**, 1193; 1933, **55**, 3669; 1936, **58**, 27), all the work of the latter authors involving the use of chloroamine. In contrast to the experience of Coleman and his colleagues with chloroamine the yields with bromides were slightly better than when using the corresponding chlorides, but the result with *iso*amyl iodide confirms the conclusions of all previous investigators that the use of iodides in this type of reaction is to be avoided. No explanation of this phenomenon could be found, all attempts, for example, to correlate the yield of amine with the relative proportions of RMgX and R_2Mg in the Grignard solution being unavailing.

The method finally adopted and exemplified by *tert.*-butylamine in the experimental section is rapid and easy to operate, and permits the facile preparation of a number of primary amines which are otherwise difficult to prepare. A further advantage is that the products are free from secondary and tertiary amines, although ammonia always appears to be formed.

	% Yield R·NH_2.				% Yield R·NH_2.		
Halide.	Present authors.	Sheverdina and Kocheshkov.	Coleman *et al.*	Halide.	Present authors.	Sheverdina and Kocheshkov.	Coleman *et al.*
Ethyl bromide	81 *	66·6 *	27·7 *	*iso*Amyl chloride	60	80·1 *	55·2
n-Propyl bromide	85 *	—	27·0 *	*iso*Amyl bromide	71	—	—
n-Butyl chloride	58	—	58·9	*iso*Amyl iodide	Trace	5·3 *	10·9
n-Butyl bromide	63	—	27·2	*tert.*-Amyl chloride ...	48	—	66·2
*iso*Butyl bromide	90	—	—	Allyl bromide	40	—	—
tert.-Butyl chloride ...	70	73·6 *	60·2	Benzyl chloride	57	—	92
n-Amyl chloride	46	—	—	2-Phenylethyl chloride	68	—	74·0
n-Amyl bromide	65	—	—	Cinnamyl chloride ...	Trace	—	14

* Isolated as, and yields calculated on, hydrochlorides.

In addition to the mono-halides listed in the Table experiments were carried out with pentamethylene bromide, hexamethylene bromide, and decamethylene bromide. In agreement with the work of Hilper and Grüttner (*Ber.*, 1914, **47**, 178) and of Bygdén (*Ber.*, 1915, **48**, 1238) it was found that attempts to form the Grignard compounds under normal anhydrous conditions resulted in the formation of highly polymerised compounds

completely unreactive towards *O*-methylhydroxylamine which was recovered unchanged. When, however, a small quantity of water was present, as suggested by Bygdén (*loc. cit.*), the normal Grignard compounds were formed, and these reacted readily with *O*-methylhydroxylamine. The optimum quantity of water required in the ether was found to be 0·1%. Under these conditions the yields of cadaverine, hexamethylenediamine, and decamethylenediamine were respectively 68%, 51%, and 53% calculated on *O*-methylhydroxylamine; the method provides a convenient means of preparation of this type of compound.

Experimental.

tert.-*Butylamine*.—A solution of *O*-methylhydroxylamine (Traube, Ohlendorf, and Zander, *Ber.*, 1920, **53**, 1477) (141 g., 3 mols.) in anhydrous ether (300 c.c.) was added gradually with vigorous stirring to a solution of *tert.*-butylmagnesium chloride (from 609 g. of *tert.*-butyl chloride) in ether (3 l.), the internal temperature during the addition being maintained at −10° to −15°. After addition was complete the temperature was kept at −10° for a further ½ hour, then allowed to rise slowly to room temperature, and the reaction mixture finally refluxed for 2 hours. It was then cooled and treated at 0° with 5N- hydrochloric acid (3 l.), the layers were separated, and the aqueous solution was evaporated to small bulk under reduced pressure. The residue, containing *tert.*-butylamine hydrochloride, magnesium chloride, and a little ammonium chloride, was strongly basified with 50% aqueous potassium hydroxide and the *tert.*-butylamine distilled out, the fraction b. p. 35—70° being collected. The crude amine was dried (KOH) and redistilled. Yield, 153 g. B. p. 40—45°. The amine after several distillations had b. p. 44·4°, $d_4^{20°}$ 0·6951, $n_D^{20°}$ 1·3789. The following were prepared: N-*Benzoyl* derivative, needles from alcohol, m. p. 134° (Found: N, 7·8. $C_{11}H_{15}ON$ requires N, 7·8%). *Picrate*, prepared in benzene; needles from ethyl acetate–chloroform, m. p. 197—198° (Found: C, 39·7; H, 4·9; N, 18·4. $C_{10}H_{14}O_7N_4$ requires C, 39·7; H, 4·7; N, 18·6%). *Styphnate*, prepared in alcohol; rhombs from alcohol, m. p. 248—250° (decomp.) (Found: C, 43·0; H, 6·5; N, 17·9. $2C_4H_{11}N, C_6H_3O_8N_3$ requires C, 43·0; H, 6·4; N, 17·9%). *Picrolonate*, prepared in benzene; needles from ethyl acetate–alcohol, m. p. 260° (decomp.) (Found: C, 50·1; H, 5·9; N, 20·4. $C_{14}H_{19}O_5N_5$ requires C, 49·9; H, 5·7; N, 20·7%).

n-*Butylamine*.—The yield of amine, b. p. 77—78°, prepared as above, was 63% from *n*-butyl bromide, or 58% from the chloride. The *picrate* crystallised from ethyl acetate–benzene in needles, m. p. 145° (Found: C, 39·9; H, 4·7; N, 18·6. $C_{10}H_{14}O_7N_4$ requires C, 39·7; H, 4·7; N, 18·6%). The *picrolonate* separated from ethyl acetate in needles, m. p. 219—220° (Found: C, 50·0; H, 5·7; N, 20·7. $C_{14}H_{19}O_5N_5$ requires C, 49·9; H, 5·7; N, 20·7%).

iso*Butylamine*.—Prepared in 90% yield from *iso*butyl bromide. B. p. 68—69°. The *picrate* crystallised from ethyl acetate–benzene in needles, m. p. 150° (Found: C, 40·2; H, 4·7; N, 18·4. $C_{10}H_{14}O_7N_4$ requires C, 39·7; H, 4·7; N, 18·6%). The *picrolonate* crystallised from ethyl acetate in needles, m. p. 215—216° (Found: C, 49·5; H, 5·9; N, 20·6. $C_{14}H_{19}O_5N_5$ requires C, 49·9; H, 5·7; N, 20·7%).

n-*Amylamine*.—Prepared in 65% yield from *n*-amyl bromide or 46% from the chloride. B. p. 104°. The *picrate* crystallised from ethyl acetate–benzene in needles, m. p. 138—139° (Found: C, 42·0; H, 4·6; N, 17·4. $C_{11}H_{16}O_7N_4$ requires C, 41·7; H, 5·1; N, 17·7%). The *picrolonate* crystallised from ethyl acetate in needles, m. p. 198° (Found: C, 51·5; H, 6·1; N, 19·7. $C_{15}H_{21}O_5N_5$ requires C, 51·3; H, 6·0; N, 19·9%).

iso*Amylamine*.—Obtained in 71% yield from the corresponding bromide or 60% from the chloride. B. p. 95—96°. *Picrate*, needles from ethyl acetate–benzene, m. p. 137·5° (Found: C, 41·5; H, 5·3; N, 17·4. $C_{11}H_{16}O_7N_4$ requires C, 41·7; H, 5·1; N, 17·7%). The *picrolonate* crystallised from ethyl acetate in needles, m. p. 219° (Found: C, 51·6; H, 6·1; N, 19·6. $C_{15}H_{21}O_5N_5$ requires C, 51·3; H, 6·0; N, 19·9%).

tert.-*Amylamine*.—The yield from *tert.*-amyl chloride was 48%. B. p. 77—78°. The *picrate* crystallised from ethyl acetate–benzene in needles, m. p. 182—183° (Found: C, 42·0; H, 5·2; N, 17·4. $C_{11}H_{16}O_7N_4$ requires C, 41·7; H, 5·1; N, 17·7%).

Allylamine.—Allyl bromide gave a 40% yield of the amine, b. p. 58°. It was characterised as its picrate, m. p. 140° (Gabriel and Eschenbach, *Ber.*, 1897, **30**, 1125, give m. p. 140—141°).

Benzylamine.—The yield of amine, b. p. 90°/12 mm., prepared from the chloride by the above method was 57%. No reason could be found for this yield being so much lower than that obtained with chloroamine (Coleman *et al.*, *loc. cit.*). The amine was identified as its picrate, m. p. 194° (Moureu and Lazennec, *Bull. Soc. chim.*, 1906, **35**, 1183, give m. p. 194°).

2-*Phenylethylamine*.—The yield of this amine, b. p. 76—78°/10 mm., prepared from the chloride, was 68%. It was characterised as the picrate, m. p. 167° (Kolshorn, *Ber.*, 1904, **37**, 2484, gives m. p. 167—168°).

Cadaverine.—Pentamethylene bromide (23 g.) was added gradually with stirring to magnesium turnings (7·6 g.) in ether (150 c.c.) containing 0·1% of water. The mixture was cooled so that the ether was just refluxing, and when the reaction had moderated the reaction mixture was kept overnight at room temperature and then refluxed for 4 hours. It was then cooled to −15° and a solution of *O*-methylhydroxylamine (4·7 g.) in dry ether (15 c.c.) was added gradually with stirring, the temperature being maintained between −10° and −15°. After addition of the *O*-methylhydroxylamine was complete, the reaction mixture was allowed to attain room temperature and then refluxed for 2 hours. The complex was decomposed with 5N-hydrochloric acid at 0°, the aqueous layer separated and made alkaline with 40% aqueous sodium hydroxide, and the diamine steam-distilled out. The distillate was made acid with hydrochloric acid and evaporated to dryness under reduced pressure, and the residue extracted with alcohol containing a trace of water. Evaporation of the alcohol gave the cadaverine hydrochloride; the free amine was liberated by means of 50% aqueous potassium hydroxide, dried over solid potassium hydroxide, and distilled. B. p. 178—180°. Yield 68%. The dipicrate crystallised from water in needles, m. p. 237° (decomp.) [Baumann and Udránszky, *Z. physiol. Chem.*, 1889, **13**, 570, give m. p. 220—222° (decomp.)].

Hexamethylenediamine.—Prepared from hexamethylene bromide as for cadaverine. B. p. 204°. Yield, 51%. The picrate crystallised from water in needles, m. p. 220° (decomp.) [Ssolonina, *Bull. Soc. chim.*, 1896, **16**, 1880, gives m. p. *ca.* 220° (decomp.)].

Decamethylenediamine.—Prepared in 53% yield from decamethylene bromide in the same way as cadaverine. M. p. 60°. The *picrate* crystallised from water in needles, m. p. 134° (Found: C, 42·0; H, 4·5; N, 17·4. $C_{22}H_{30}O_{14}N_8$ requires C, 41·9; H, 4·8; N, 17·7%).

The authors wish to thank Mr. A. Copple and Miss D. Lofthouse for assistance and the Chief Scientific Officer, Ministry of Supply, for permission to publish this work.

Research Establishment, Sutton Oak. [*Received, March 4th*, 1946.]

162. *Methylation of β-Methylglucopyranoside and αβ-Methylxylopyranosides by Thallous Hydroxide and Methyl Iodide.*

By C. C. Barker, E. L. Hirst, and J. K. N. Jones.

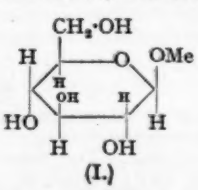
Methylation of β-methyl-*d*-glucopyranoside by the thallous hydroxide–methyl iodide process gives some of the fully methylated product, in addition to trimethyl β-methyl-*d*-glucopyranoside, when excess of thallous hydroxide is used in the formation of the thallium derivative of the sugar. The trimethyl β-methyl-*d*-glucopyranoside fraction contains all the four possible isomers (2 : 4 : 6; 2 : 3 : 6; 2 : 3 : 4; 3 : 4 : 6, with the 2 : 4 : 6 derivative preponderating), in proportions similar to those obtained by the methylation of α-methyl-*d*-glucoside by the thallous hydroxide–methyl iodide process (Barker, Hirst, and Jones, *J.*, 1938, 1695). The position of the methoxyl group on C_1 in methylglucopyranoside does not, therefore, significantly affect the orientation taken up by the thallium atoms in the formation of trithallium methyl-*d*-glucopyranoside.

Methylation of a mixture of α- and β-methyl-*d*-xylosides by the same process gives trimethyl methyl-*d*-xyloside and dimethyl methyl-*d*-xyloside. The dimethyl methyl-*d*-xyloside is a mixture of all three possible sugars in which 2 : 4-dimethyl methyl-*d*-xyloside predominates. In view of the bulky nature of the thallium atom and the spatial position of the hydroxyl groups, these results are in agreement with expectation and similar to those obtained in the methylation of the methyl-*d*-glucopyranosides.

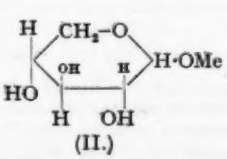
It has already been shown that methylation of α-methyl-*d*-glucopyranoside (I) by means of the thallous hydroxide–methyl iodide method (Menzies, *J.*, 1926, 937) gives tetramethyl α-methyl-*d*-glucopyranoside and trimethyl α-methyl-*d*-glucoside. The latter was a mixture of all four possible isomers (Barker, Hirst, and Jones, *loc. cit.*), in the proportions 2 : 4 : 6-trimethyl *d*-glucose, *ca.* 50%; 2 : 3 : 6-trimethyl *d*-glucose, *ca.* 36%; 3 : 4 : 6-trimethyl *d*-glucose, *ca.* 10%; 2 : 3 : 4-trimethyl *d*-glucose, *ca.* 4%.

The methylation of β-methyl-*d*-glucopyranoside (I) by thallous hydroxide–methyl iodide has now been shown to follow a very similar course; the trimethyl β-methylglucoside fraction contains all four isomers in the following proportions: 2 : 4 : 6, *ca.* 62%; 2 : 3 : 6, *ca.* 20%; 3 : 4 : 6, *ca.* 15%; and 2 : 3 : 4, *ca.* 3%. In both cases the amount of 2 : 4 : 6-trimethyl methylglucoside preponderated. This procedure can be utilised as a method for the preparation of the somewhat inaccessible 2 : 4 : 6-trimethyl glucose. Comparison of these figures with those obtained when the α-methylglucoside was methylated show that, within the limits of experimental error, the position of the glycoside methoxyl had little effect upon the positions taken up by the thallium atoms in the original trithallium methylglucoside.

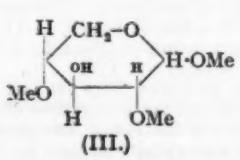
Xylopyranose differs from glucopyranose only in the absence of a side chain on C_6. It was of interest, therefore, to determine the positions taken up by the thallium atoms in the methylation of methyl-*d*-xyloside by the thallium hydroxide method. Since preparations of pure α- or β-methyl-*d*-xyloside are not readily available and the position of the glycosidic methoxyl group in the methylglucosides had little, if any, effect on the positions occupied by the thallium atoms, a mixture of α- and β-methylxylopyranosides, containing some 42% of the α-derivative, was used in the present experiments. An examination of the structural formula of



(I.)



(II.)



(III.)

methyl-*d*-xyloside (II) shows that the hydrogen atoms on the hydroxyl groups on C_2 and C_4 are most likely to be substituted since they are the greatest distance apart, and the thallium atoms in these positions are therefore least likely to interfere with one another. 2 : 4-Dimethyl methyl-*d*-xyloside (III) is therefore likely to be formed preferentially, and the experimental results showed that this was indeed the case. 2 : 4-Dimethyl xylose has not hitherto been prepared but the method now described renders it reasonably accessible. Proof of its structure rests on the following observations. (*a*) It is not identical with either of the known dimethyl xylopyranoses (2 : 3- and 3 : 4-). (*b*) On oxidation with bromine it yields a *pyranolactone*, the amide from which gives a negative Weerman test. Methyl groups are therefore present on C_2 and C_4.

Experimental.

Methylation.—β-Methylglucoside (m. p. 105°; $[\alpha]_D^{20°}$ −34° in water, *c*, 1·0) (24·7 g.) was dissolved in water (15 c.c. and added to a solution of 1·6N-thallous hydroxide (600 c.c.) which had been concentrated to a small volume (about 100 c.c.). The precipitate was filtered off, washed, dried, and then digested with boiling methyl iodide (for further details see Barker, Hirst, and Jones, *loc. cit.*). A syrup (24·3 g.), $n_D^{20°}$ 1·4462, was isolated and distilled in a vacuum giving the following fractions:

Fraction I. Tetramethyl β-methylglucoside (14·32 g.) (Found: OMe, 60·8%).
Fraction II. Mixed methylated methylglucosides (2·86 g.) (Found: OMe, 57·7%).
Fraction III. Trimethyl β-methylglucoside (5·19 g.) (Found: OMe, 51·2%).
Residue. 1·39 g.

Fraction III crystallised. A portion (3·69 g.) was recrystallised from light petroleum (b. p. 40—60°) and gave 2 : 4 : 6-trimethyl β-methylglucoside (1·32 g.), m. p. 66°; mixed m. p. with an authentic specimen, 67°. The residual syrup (2·12 g.) was hydrolysed with 8% hydrochloric acid and the sugar (*A*) (1·62 g.) was isolated in the usual manner.

Estimation of 2 : 3 : 6-*Trimethyl Glucose in the Syrup* (*A*).—A portion of the syrup dissolved in 1% methyl alcoholic hydrogen chloride showed $[\alpha]_D^{20°}$ +72° (initial value); +69° (½ hour); 66° (1 hour); 61° (2 hours); 55° (3 hours); 51° (4 hours); 46° (6 hours); 43° (7·5 hours); 40° (9 hours); 38° (constant value, 24 hours). Under similar conditions 2 : 3 : 6-trimethyl *d*-glucose shows a change from $[\alpha]_D^{20°}$ +73° to −31°; this gives 32% as the amount of 2 : 3 : 6-trimethyl *d*-glucose present in the syrup (*A*). (Calc. on the weight of Fraction III, 20%.)

Estimation of 3 : 4 : 6-*Trimethyl* d-*Glucose*.—A portion of the syrup (*A*) was oxidised with bromine water and the resultant mixture of lactones isolated in the usual manner after distillation. (Yield 83%; Found: OMe, 41·5; equiv. wt., 217. Calc. for $C_9H_{16}O_6$: OMe, 42·3%; equiv. wt., 220.) The lactones were converted into the amides by solution in liquid ammonia. The mixed amides (51 mg.) gave, on treatment with sodium hypochlorite followed by semicarbazide, the hydrazodicarbonamide (2·4 mg.), which, assuming a 40% yield in the reaction (see Hirst and Jones, *J.*, 1938, 496), implies the presence of 24% of 3 : 4 : 6-trimethyl *d*-glucose in syrup *A*, or 15% calculated on Fraction III.

Estimation of 2 : 3 : 4-*Trimethyl* d-*Glucose*.—This estimation was carried out by the method used previously. The mixed glucosides (1·35 g.) gave silver iodide (0·047 g.), after the *p*-toluenesulphonyl derivatives had been heated with sodium iodide, equivalent to the presence of 3% of the 2 : 3 : 4-isomer. From the above mentioned evidence the yields of the various isomerides were as follows:

2 : 4 : 6-Trimethyl β-methyl-*d*-glucoside (isolated as crystalline glucoside) (*ca.* 36%).
2 : 3 : 6-Trimethyl β-methyl-*d*-glucoside (*ca.* 20%).
2 : 3 : 4-Trimethyl β-methyl-*d*-glucoside (*ca.* 3%).
3 : 4 : 6-Trimethyl β-methyl-*d*-glucoside (*ca.* 15%).

The remainder (*ca.* 26%) consisted of 2 : 4 : 6-trimethyl β-methylglucoside which failed to crystallise and was not directly estimated.

The Action of Thallium Hydroxide on Methyl-d-*xyloside*.—Xylose was boiled under reflux with methyl alcoholic hydrogen chloride and the resulting mixture of methylxylopyranosides isolated in the usual manner and purified by distillation in a vacuum. B. p. 180°/0·01 mm. (bath temp.); $[\alpha]_D^{19°}$ +62° in water. The mixed xylosides (36·9 g.) were evaporated to dryness with 1·54N-thallous hydroxide (2·5 equivalents) under reduced pressure and in a stream of carbon dioxide-free air. The yellow thallium derivative thus obtained was dried, powdered, and converted into a mixture of methylated xylosides by boiling under reflux with excess of methyl iodide.

The methylated xylosides (40·6 g.) isolated in the usual manner were fractionally distilled giving:

Fraction I. Trimethyl methyl-*d*-xylosides (13·72 g.) (Found: OMe, 62·0%).
Fraction II. Dimethyl methyl-*d*-xylosides (20·0 g.) (Found: OMe, 48·3%).
Fraction III. Still residue, 6·90 g.

Fraction II (20·0 g.) was heated at 100° with 8% hydrochloric acid for 70 minutes; the solution was cooled, neutralised with barium carbonate, filtered, and evaporated to dryness. The dimethyl *d*-xylose was taken up in ether and was obtained as a syrup (16·9 g.) which partly crystallised. Trituration with acetone–light petroleum (b. p. 40—60°) gave β-2 : 4-*dimethyl* d-*xylose* (3·0 g.), m. p. 108° (Found: C, 47·2; H, 7·9; OMe, 34·8. $C_7H_{14}O_5$ requires C, 47·1; H, 7·9; OMe, 34·5%). In aqueous solution the sugar showed mutarotation as follows: $[\alpha]_D^{20°}$ −30° (initial value); −16° (7 mins.); −8° (10 mins.); −1° (15 mins.); +4° (20 mins.); 9° (25 mins.); 13° (30 mins.); 15° (40 mins.); 19° (55 mins.); 22° (constant value, 24 hours).

On boiling with alcoholic aniline, the sugar gave 2 : 4-*dimethyl* d-*xylose anilide*, m. p. 170°; $[\alpha]_D^{20°}$ −82° (in dioxan) (Found: C, 61·4; H, 7·7; N, 5·5; OMe, 23·3. $C_{13}H_{19}O_4N$ requires C, 61·8; H, 7·5; N, 5·8; OMe, 24·5%). Oxidation of the sugar (1 g.) with bromine (1 c.c.) in water (6 c.c.) at 50° for 4 hours gave 2 : 4-*dimethyl* d-*xylonic acid* isolated, in the usual manner, as a syrup which on distillation in a vacuum gave 2 : 4-*dimethyl* d-*xylopyranolactone*, $n_D^{20°}$ 1·4768; $[\alpha]_D^{20°}$ +23° (in chloroform). The lactone mutarotated in water at a rate characteristic of a pyranolactone, $[\alpha]_D^{20°}$ −15° (initial value); −13° (1 hour); −11° (2 hours); −9° (3 hours); −6° (5 hours); +19° (23 hours); +28° (45 hours); +30° (constant value). (Found: C, 47·7; H, 7·0; OMe, 34·8; equiv. wt., 176. $C_7H_{12}O_5$ requires C, 47·7; H, 6·9; OMe, 35·2%; equiv. wt., 176).

The amide, prepared from the lactone by dissolving it in liquid ammonia and allowing excess ammonia to evaporate, was a syrup which gave a negative Weerman reaction proving the presence of a methoxyl group on C_2.

Examination of the Syrup Remaining after Removal of Crystalline 2 : 4-*Dimethyl* d-*Xylose*.—The mixed lactones were prepared fom the syrupy sugars by the usual method (yield, 80%) (Found: OMe, 35·0; equiv. wt., 173. Calc. for $C_7H_{12}O_5$: OMe, 35·2%; equiv. wt., 176). $[\alpha]_D^{20°}$ +17° ⟶ + 47° (48 hours, constant value).

Reaction of the mixed lactones with liquid ammonia gave a non-crystalline mixture of amides which gave a positive Weerman reaction. The mixed amides (73 mg.) were treated with sodium hypochlorite followed by the addition of semicarbazide after the removal of excess of hypochlorite. The precipitated hydrazodicarbonamide was filtered off, dried, and weighed (yield, 7·6 mg.). This corresponds to the presence of some 8% of 3 : 4-dimethyl *d*-xylose in Fraction II (above) assuming a yield of 40% of the theoretical in the yield of hydrazodicarbonamide.

2 : 3-Dimethyl *d*-xylonolactone mutarotates in water from $[\alpha]_D^{20°}$ +97° ⟶ + 86° (48 hours), 2 : 4-dimethyl *d*-xylonolactone from $[\alpha]_D^{20°}$ −15° ⟶ + 30° (equilibrium value), and the 3 : 4-isomer from $[\alpha]_D^{20°}$ −56° ⟶ − 34° (48 hours) ⟶ −27° (equilibrium value) (James and Smith, *J.*, 1945, 744) in 65 hours. These rotational figures (equilibrium values) taken in conjunction with the estimated yield of 3 : 4-dimethyl *d*-xylose (from the yield of hydrazodicarbonamide) indicate the presence of some 39% of 2 : 3-dimethyl *d*-xylose in the syrup or of 32% of the sugar in Fraction II.

These results indicate that the dimethyl methylxyloside fraction contains the following sugars in the approximate percentages indicated:

2 : 4-Dimethyl *d*-xylose. Isolated as crystals (*ca.* 18%).
2 : 4-Dimethyl *d*-xylose. Non-crystalline, by difference (*ca.* 43%).
3 : 4-Dimethyl *d*-xylose. From yield of hydrazodicarbonamide in Weerman test (*ca.* 7%).
2 : 3-Dimethyl *d*-xylose. From lactone formation (*ca.* 32%).

In view of the uncertainty concerning the optical rotatory power of 3 : 4-dimethyl *d*-xylonolactone (cf. Mullen and Percival, *J.*, 1940, 1504) the percentages given above are regarded as approximate only and the proportion of the 2 : 4-isomeride may be some 8% higher than that stated. The general position, however, remains unaltered.

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163. *Chromatographic "Spot" Tests.*

By P. P. Hopf.

A piece of filter-paper, when treated with an adsorbent, preferably peptised alumina, and incorporating a developer, will act like a chromatographic column towards a solution containing constituents suitable to the developer, and exhibit coloured zones, specific to the constituent, solvent, developer, and pH only. These zones are suitable for comparative analysis. The order of such zones is not the chromatographic series, for the mobility of the constituent in question may be that of an ion, molecule, or newly formed complex.

Flood's formula (*Z. anal. Chem.*, 1940, **120**, 327) has been found to hold in most cases.

It has been shown by Flood (*loc. cit.*) that filter-paper, when treated with sodium aluminate in such a manner that alumina is precipitated on the fibre, exhibits selective adsorption and behaves with inorganic solutions in a manner similar to a chromatographic column as shown by Schwab (*Angew. Chem.*, 1940, **53**, 39). Papers may, however, be treated with other adsorbents to acquire these properties. For instance, blotting-paper, *i.e.*, paper containing fuller's earth, has been found satisfactory, provided it be smooth, for loose fibres, by creating capillary forces in different directions, cause considerable variation in the behaviour of the paper towards ions or constituents normally travelling in a direction away from the point of feeding. Starch paper was also found suitable in several instances, but papers containing silica gel have not been found effective. The adsorptive properties of the paper are not impaired by dyeing the whole sheet by immersion in an organic dye. It was, therefore, considered possible to include in the adsorbent paper a reagent showing coloured complexes with the constituents of a solution to be analysed. Here several distinct types of visible adsorption have to be considered, *i.e.*, those involving (*a*) coloured insoluble complexes, (*b*) coloured soluble complexes, (*c*) selective adsorption of a dye by a constituent, (*d*) constituents assuming distinctive colours of their own on separation.

Into categories (*a*) and (*b*) would fall a solution of ferromolybdenum in dilute acid. When such a solution is treated with 8-hydroxyquinoline in acetic acid solution, only the molybdenum complex is precipitated, the iron complex being soluble in acid solution. A paper treated with alumina and oxine solution and dried, when spotted with the ferromolybdenum solution will develop a yellow (Mo) central zone and a black (Fe) outer zone, the area of each being indicative of the relative amounts present. A different ferromolybdenum solution at the same pH will give an absolutely comparable result. The molybdenum here is precipitated instantly and is adsorbed as a complex, displacing the iron, which travels in ionic form and only forms the visible complex on drying.

As an example of category (*c*), a paper treated with alumina on which a mixture of amyl acetate and ethyl alcohol containing a trace of fluorescein has been spotted will show a coloured central zone and a colourless outer ring. The alcohol and the acetate travel freely, and adsorption would have taken place at the same levels without the presence of the dye; the latter, being insoluble in amyl acetate, remained with the alcohol. Again, good and comparable results were obtained on repetition.

The most suitable paper for constant results was obtained by using a colloidal solution of alumina prepared by peptisation of a solution of sodium aluminate with acetic acid (Weiser, *J. Physical Chem.*, 1920, **24**, 525), and air-drying the paper after immersion. In some cases, however, another adsorbent has to be used. For example, starch papers have to be used in tests specific to alkali metals; such papers, soaked in violuric acid solution and dried, will give distinctive and comparable results for mixtures of sodium, potassium, and ammonium. Here it was noted that, although the presence of any of the above did not influence the chromatographic picture of the others, which were separated by clear blank zones, yet the pH has to be very strictly controlled, as this reagent forms different complexes in neutral and in acid solution, the results from neutral solutions being very difficult to observe, owing to less intensive colours.

For simple investigations, Flood's formula zone radius $= f(\log c + A)$, where c = concentration and A is a constant for the paper, is valid. It will, however, be found that, as the pH influences the size of all zones, a specific constant for each constituent at a definite pH and for a specific paper has to be found empirically. When only comparative results are required, *i.e.*, when the course of a reaction is to be continuously observed, the knowledge of this constant is unnecessary. It was found that the slightest variation in the preparation of the papers influenced the constant considerably. The dependence on the pH varied with the sensitivity of the reagent or developer incorporated.

If a solution contains constituents A and B, three drops (say) of the solution are placed on a suitable paper at regular intervals during the reaction, giving two ring-like zones, the first one (for A) being bounded by radii r_1 and r_2, and the second for B by radii r_3 and r_4 (if B = Mo on an oxine paper, $r_4 = 0$). If the two rings are not separated by a blank zone, $r_2 = r_3$. If the initial solution is of known concentrations a and b, respectively, then

$$a = (r_1^2 - r_2^2)K_a\pi \text{ and } b = (r_3^2 - r_4^2)K_b\pi$$

and the values of K_a and K_b may be calculated. If, however, the first test is denoted by suffix α, and the next one by β, the variation may be obtained by direct measurement:

$$a_\alpha/a_\beta = (r_{1\alpha}^2 - r_{2\alpha}^2)/(r_1^2\beta - r_2^2\beta)$$

Further, from the above, we have

$$a/b = (r_1^2 - r_2^2)K_{a/b}/(r_3^2 - r_4^2), \text{ where } K_{a/b} = K_a/K_b.$$

For illustration, the following table shows some separations which are easily achieved on such papers. The adsorbent was peptised alumina in all cases except that of Na/K/NH_4, for which it was starch.

Constituents.	Developer solution.	Remarks.
Fe/Mn	Formaldoxime hydrochloride	3% Of ferromanganese, just acid. Expose to NH_3 vapour after drying
Fe/Mo/V/Ti	5% Oxine in 10% acetic acid	1% Metals, just acid
Ni/Co	Nitrosonaphthol and dimethylglyoxime, aqueous	Any concentration, strongly acid
Na/K/NH_4	Violuric acid, aqueous	Buffered acetic acid solution
Ketones, aldehydes, and cyclic carboxyl compounds	2 : 4-Dinitrophenylhydrazine, 2% in acetic acid	Alcoholic solution or solvent-free mixtures
Cu/Ni/Fe/Cr (VI)	α-Benzoinoxime, 2% in alcohol	Nearly neutral. Expose to NH_3 vapour when dry

Experimental.

Selection of Paper.—The paper was tested by dissolving 5 g. in 5 c.c. of sulphuric acid and heating the solution to fuming (hot plate) with sufficient nitric acid to destroy organic matter. The mixture was diluted to 100 c.c. and filtered. After neutralisation with ammonia the solution should give no colour change or precipitate with oxine solution. A paper having passed this test is dipped into water in such a way that one inch is submerged and 3 inches remain clear: if the paper is suitable, the water should be drawn up to 2 inches above the surface by capillary forces within one minute.

Preparation of Paper.—The paper is dipped in a peptized alumina solution (as above) or into fairly concentrated hot starch solution. Alternatively, it is dipped in sodium aluminate solution, dried, and dipped in sodium carbonate solution. In each case it is washed for 5 hours at 20—25° with stirring, soaked in the chosen developer, washed by immersion in water, and air-dried at room temperature.

Analysis of Ferromanganese.—A paper prepared with peptised alumina and formaldoxime hydrochloride solution is used. The test solution is made to contain about 3% of metal and is neutralised with ammonia to incipient precipitation. A standard stain with a metal of Fe/Mn = 0·01081 gives $r_1 = 39{\cdot}17$ mm., $r_2 = 34{\cdot}00$ mm., $r_3 = 28{\cdot}8$ mm., $r_4 = 0$. This stain is obtained by using two drops of the solution, allowing it to dry on a flat surface, and exposing it to ammonia vapour. From the above, $(r_1^2 - r_2^2)/(r_3^2) = 0{\cdot}456$, *i.e.*, $K_{Fe/Mn} = 0{\cdot}0237$. A stain of metal of unknown composition gave the radial ratio as 0·363, *i.e.*, Fe/Mn = 0·363 × 0·0237 = 0·0086. The analytical result showed the sample to have a ratio Fe/Mn = 1 : 112·5 = 0·00889.

2 : 4-Dinitrophenylhydrazones.—A paper impregnated as above and dipped in a 1% solution of the reagent in alcohol to which 5% acetic acid had been added was dried. A solution containing 10% each of methyl hexyl ketone, benzaldehyde, and acetaldehyde in ether was spotted on. Three distinct zones were obtained with benzaldehyde in the centre and acetaldehyde in the outer zone. One after the other of the constituents was reduced in area till it eventually disappeared. The zones not affected stayed constant, while those affected were reduced in area in proportion to the composition of the solution.

Alkali Metals.—A paper is treated with starch and then with a solution of violuric acid according to Erlenmeyer (*Helv. Chim. Acta*, 1941, **24**, 878). An aqueous solution containing 5% of sodium acetate, 5% of ammonium chloride, and 5% of potassium chloride, to which 2% of acetic acid has been added, is spotted on. A spot with an inner blank zone was followed by a red sodium zone ($r_4 = 0{\cdot}95$, $r_3 = 1{\cdot}50$ cm.), a pink potassium zone ($r_4 = r_3$, $r_2 = 1{\cdot}90$ cm.), a blank zone, and a blue ammonia zone ($r_2 = 2{\cdot}45$, $r_1 = 2{\cdot}475$ cm.). From these the following areas are calculated: Na = 4·24, K = 4·27, NH_4 = 4·71 cm.². By exactly halving the concentrations of ammonium chloride and potassium chloride in the same solution, the radii measured became $r_6 = 1{\cdot}25$, $r_5 = 1{\cdot}70$, $r_4 = r_5$, $r_3 = 1{\cdot}890$, $r_2 = 2{\cdot}14$, $r_1 = 2{\cdot}315$ cm. These give the following areas: Na = 4·24, K = 2·15, NH_4 = 2·40 cm.².

Ferromolybdenum.—A paper impregnated with peptised alumina and 8-hydroxyquinoline was used. 2 G. of the metal were powdered, and warmed with nitric acid till no more brown fumes appeared. 10 C.c. of concentrated hydrochloric acid were added and the mixture was evaporated to a small bulk. 15 C.c. of 18N-sulphuric acid were added, and the mixture was evaporated to fuming. After being cooled and boiled with 50 c.c. of water, the mixture was filtered, and to this solution ammonia was added till a turbidity appeared which was cleared again with sulphuric acid. On spotting, this solution gave an outer zone of black (Fe), separated from an inner yellow spot (Mo) by a blank zone. For this solution and paper, the factor $K_{Fe/Mo}$ had been found to be 0·81. A sample known to contain 73·2% of Mo, gave the factor Fe/Mo = 0·346 (actual: 0·35).

Molybdenum and Vanadium.—On a paper prepared with alumina and 8-hydroxyquinoline, comparable results have been obtained at very definite pH limits. At pH values 8—9 the vanadium is in the centre, being insoluble and instantly precipitated. At pH values 8—4 the results for the same solution stayed constant only at exactly the same pH. At stronger acidities the pH seemed no longer to exert such a strong influence, as is expected from the solubility of the two complexes.

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164. *The Solubility of Sulphur Dioxide in Fuming Sulphuric Acid.*

By F. D. Miles and T. Carson.

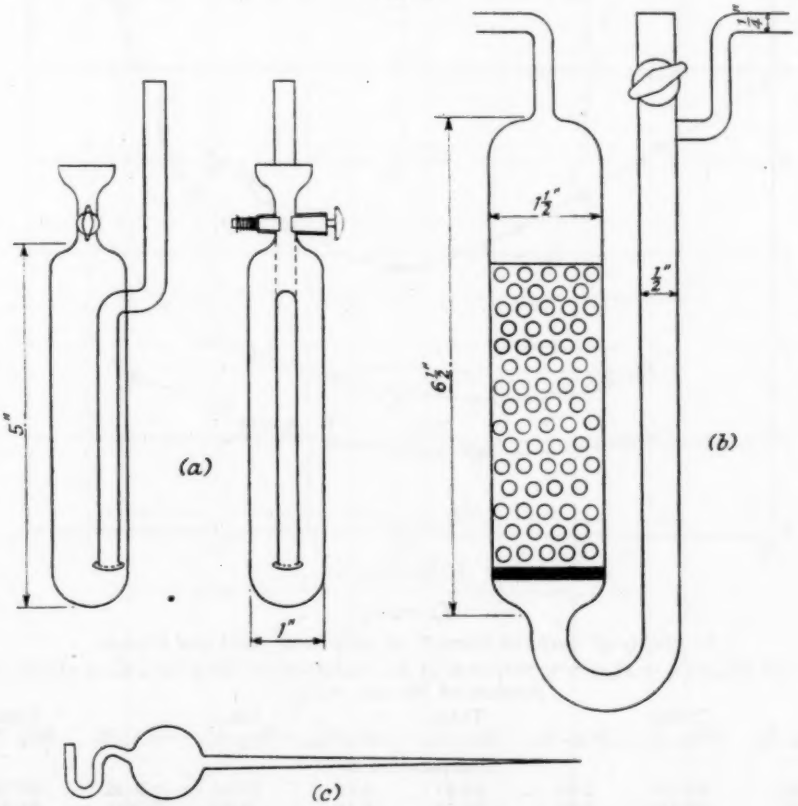
The solubilities of sulphur dioxide in fuming sulphuric acid have been determined at 20° in acid containing from 0 to 72% of free sulphur trioxide and at 40° and 60° in acid of concentration ranging from 80% H_2SO_4 to 20% free SO_3. The solubility curves show evidence of the compounds H_2SO_4,H_2O and H_2SO_4,SO_3. To obtain a rough check on the applicability of Henry's law, some measurements of the equilibrium absorption from a gas mixture containing 6% of sulphur dioxide were also made.

The solubility of sulphur dioxide in fuming sulphuric acid is of general interest and has some technical importance. "Oleum" is produced by absorption of sulphur trioxide from an atmosphere which also contains the dioxide

and, in dependence on the temperature, the concentration of the absorbing sulphuric acid, and other conditions, more or less of this gas may remain dissolved in the final product.

On the solubility of sulphur dioxide in fuming acid no data have been published. For sulphuric acid in the range 55—98% H_2SO_4 the solubilities at 20° in g. % of solution were determined by Miles and Fenton (*J.*, 1920, **117**, 59). Corresponding values at 41° and 62° were given by Cupr (*Rec. Trav. chim.*, 1928, **47**, 55) (see Fig. 2). Lopatto and Sawinaeff (*J. Appl. Chem. U.S.S.R.*, 1934, **7**, 881) investigated the composition of the sulphur dioxide–sulphuric acid mixtures which were in equilibrium with sulphur dioxide–air mixtures containing up to 24%, and occasionally up to 38%, of the dioxide, at temperatures between 20° and 60°, but they worked only with sulphuric acid concentrations in the range 62—70%. In the work reported here, many determinations were made of the solubility of the dioxide in oleum of concentrations varying from 0 to 22% of pure sulphur trioxide (81·63—95% total SO_3), and others, not so numerous as those at 20°, were carried out at 40° and 60° in the lower range from 80% H_2SO_4 to 20% free SO_3 (65—85% total SO_3). In addition, since the solubilities of sulphur dioxide determined at atmospheric pressure in the absence of air cannot be used to calculate the amount dissolved at a lower pressure, or in a dilute dioxide–air mixture, unless the amount dissolved is proportional to the partial pressure, some measurements were made of the amount of sulphur

FIG. 1.



dioxide taken up by three varieties of acid (of 80, 96, and 104% H_2SO_4) from 6% mixtures of sulphur dioxide and air, in order to find out how far Henry's law could be relied on in this case.

The whole of the experimental data for 20°, 40°, and 60°, with the exception of a single result which was obviously in error, are given in Table I and in Figs. 2 and 3. The values given on the graphs and in the second columns of the table are stated in g. of dioxide dissolved in 100 g. of acid and have been corrected to correspond with an atmosphere of dioxide at 760 mm. pressure, by multiplying each of the experimental values by the factor $760/(P-p)$, in which P is the atmospheric pressure recorded during the process of saturation, and p is the vapour pressure of sulphur trioxide above the oleum at the temperature of saturation. The values of p were taken from previous work reported by McDavid (*J. Soc. Chem. Ind.*, 1924, **43**, 57T) and by Miles, Niblock, and Wilson (*Trans. Faraday Soc.*, 1940, **36**, 345). In Fig. 2 the black dots on the uppermost graph represent the results obtained by Miles and Fenton (*loc. cit.*) for sulphuric acid of 60—100% H_2SO_4 content at 20°. The results of the present work are plotted as circles on this graph and also in Fig. 3, in which the curve is shown extended into the region of higher trioxide concentration on a rather larger scale. Besides the well-known minimum of solubility corresponding very nearly to the dihydrate of sulphur trioxide (H_2SO_4,H_2O containing 84·5% H_2SO_4), there is a distinct inflexion of the curve, which appears to fall to a minimum very nearly at the point

FIG. 2.

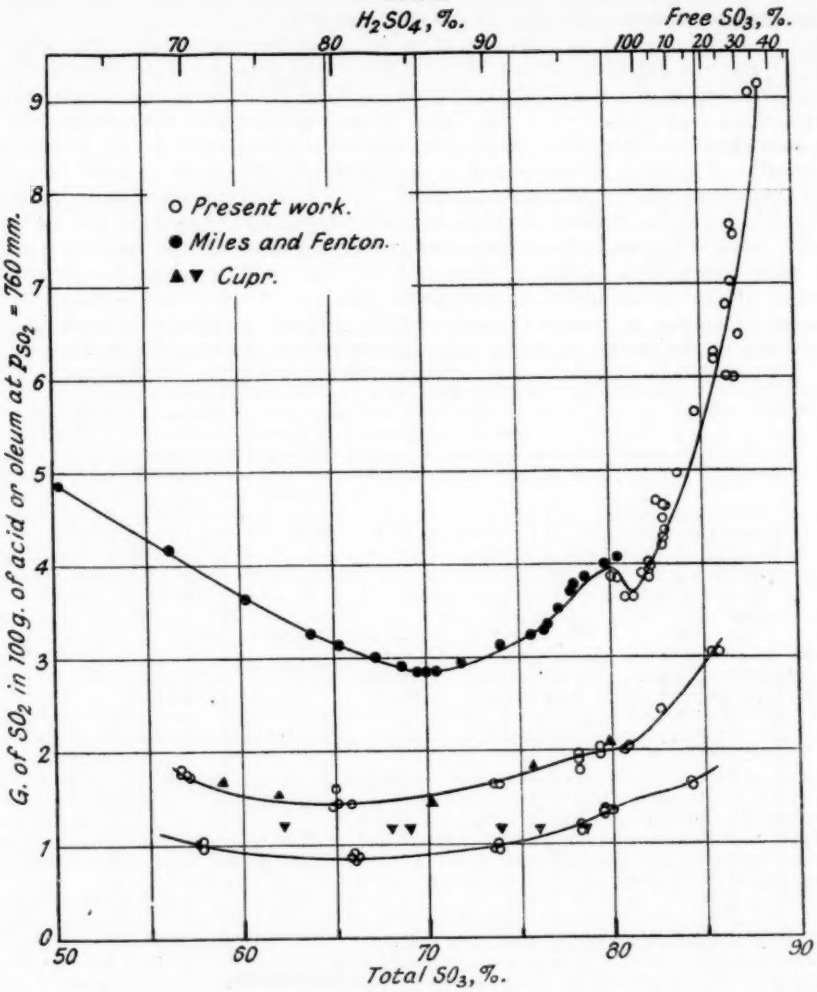


TABLE I.

Solubility of Sulphur Dioxide in Sulphuric Acid and Oleum.

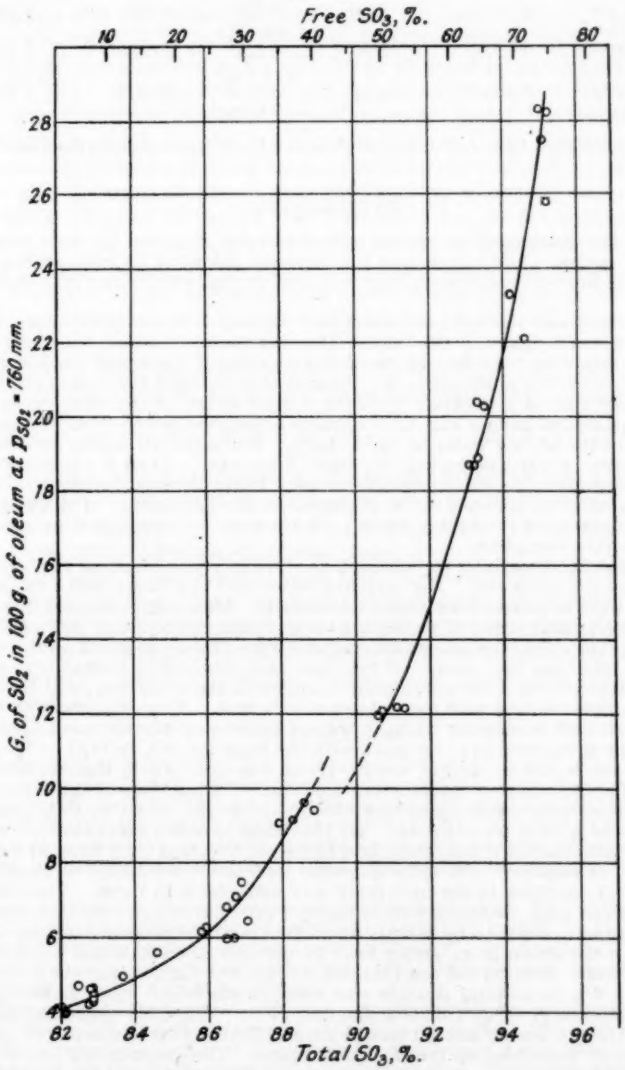
% total SO_3 = 100 $SO_3/(SO_3 + H_2O)$; % SO_2 = g. of SO_2 dissolved by 100 g. of acid or oleum, corrected for a pressure of 760 mm. of SO_2.

Total SO_3, %.	SO_2, %.	Total SO_3, %.	SO_2, %.	Total SO_3, %.	SO_2, %.	Total SO_3, %.	SO_2, %.	Total SO_3, %.	SO_2, %.
				Temperature 20°.					
80·21	3·85	82·17	3·98	84·57	5·62	87·90	9·06	93·30	18·93
80·37	3·81	82·53	4·66	85·77	6·18	88·30	9·17	93·30	20·42
80·64	3·66	82·75	4·18	85·94	6·27	88·60	9·58	93·34	20·28
80·81	3·65	82·8	4·58	86·47	6·77	88·90	9·41	94·20	23·31
81·63	3·88	82·85	4·33	86·49	5·99	90·65	11·98	94·60	22·13
82·03	3·95	82·90	4·60	86·65	5·99	90·70	12·05	95·22	25·78
82·07	3·85	82·90	4·48	86·71	7·06	91·10	12·17	95·02	27·58
82·12	3·91	82·91	4·28	86·93	7·52	91·30	12·14	95·10	28·34
82·13	3·96	83·65	4·96	87·11	6·47	93·16	18·73	95·23	28·16
				Temperature 40°.					
56·75	1·798	64·99	1·602	73·70	1·634	79·39	2·035	85·0	3·176
56·90	1·747	65·04	1·406	78·15	1·920	79·52	2·050	85·0	3·132
56·90	1·764	65·13	1·431	78·20	1·792	80·80	2·020	—	—
57·0	1·712	65·87	1·406	78·20	1·928	80·95	2·050	—	—
57·05	1·702	73·64	1·628	79·38	1·981	82·70	2·468	—	—
				Temperature 60°.					
57·75	0·983	66·03	0·834	73·82	0·953	79·50	1·346	84·30	1·625
57·9	0·986	66·14	0·848	73·87	0·990	79·57	1·337	84·40	1·610
57·91	0·988	66·23	0·858	78·22	1·196	79·60	1·359	—	—
65·88	0·855	73·75	0·949	78·31	1·172	79·90	1·371	—	—

corresponding to the composition of the monohydrate (H_2SO_4). As trioxide is added to its monohydrate, the solubility of the dioxide rises very steeply. At about 50% of free trioxide, *i.e.*, at a point close to the composition of pyrosulphuric acid (free $SO_3 = 45\%$), there is evidence of another slight but unmistakable inflection.

The solubilities at 40° and 60° were measured over a narrower range—from 70% H_2SO_4 to 20% oleum—chosen to include most of the acids of technical importance. The two curves show the same general relation as before; the principal minimum is apparent, although at a lower SO_3/H_2O ratio, and there are distinct bends in the neighbourhood of the monohydrate. The points marked by triangles represent the results obtained by

FIG. 3.



Cupr at 41° and 62°. A line drawn through his points at 60° would be straight and horizontal to an improbable degree.

The results of the determinations of the absorption of dioxide from mixtures of this gas and air are given in Table II. Only average results are stated, each being the mean of 3—6 determinations from separate experiments. Three concentrations of acid—80·2% H_2SO_4, 96·5% H_2SO_4, and an oleum containing 17·8% of free SO_3—were used. The gas mixture chosen was one of 6·0% of dioxide and 94% of air. The last column of each section of the table gives the ascertained weight of dioxide in 100 g. of acid, corrected to correspond to a pressure of 0·06 × 760 mm. of dioxide. The middle column of each section gives the calculated weight as $0{\cdot}06S$, S being the solubility, already stated in Table I, in g. of dioxide/100 g. of acid at 760 mm. pressure of the dioxide. The determined and calculated figures agree fairly well at 20°. At this temperature the assumption of Henry's law in calculating the absorption of the dioxide from any plant gas mixture would not lead to serious error, but at higher temperatures the calculated amounts of absorption are less than the experimental figures show, by an amount which is on the average about 10% at 40° and 15% at 60°.

TABLE II.

Comparison of actual and calculated absorption of sulphur dioxide from a 6% gas mixture by sulphuric acid at 20°, 40°, and 60°.

	80·2% H_2SO_4; 65·4% total SO_3.			96·5% H_2SO_4; 78·6% total SO_3.			104·0% H_2SO_4; 17·8% free SO_3.		
Temp.	*S*, g./100 g. of acid.	0·06*S*.*	G. of SO_2/100 g. of acid (found).	*S*, g./100 g. of acid.	0·06*S*.*	G. of SO_2/100 g. of acid (found).	*S*, g./100 g. of acid.	0·06*S*.*	G. of SO_2/100 g. of acid (found).
20°	3·10	0·186 (−0·54%)	0·187	3·80	0·228 (+2·7%)	0·222	5·70	0·342 (0·0%)	0·342
40	1·43	0·086 (−11·7%)	0·0974	1·95	0·117 (−7·2%)	0·1260	2·90	0·174 (−9·9%)	0·193
60	0·85	0·051 (−20·0%)	0·0637	1·28	0·0768 (−11·0%)	0·0863	1·74	0·105 (−12·5%)	0·120

* Percentages show the difference between determined results and those calculated from the solubility of pure SO_2, as a proportion of the former.

EXPERIMENTAL.

Apparatus and Method.—The absorber (Fig. 1*a*) was a glass vessel 5″ long and 1¼″ wide, closed by a large tap, the plug of which was secured by a spring. The cup above the tap was intended to make filling easier, but proved to be unnecessary. The gas-leading tube entered through the side, and its end was blown into a bulb perforated with a number of fine holes.

The acid or oleum was poured into the dry absorption tube through a funnel with a long thin stem, inserted through the bore of the stopcock, and was weighed in the tube. The thermostat in which the absorber was clamped was filled with clear transformer oil to minimise the effect of the oleum escaping if the vessel cracked or broke. Sulphur dioxide from a siphon was passed in through the inlet tube. To a branch tube between the siphon and the absorber was connected a pressure regulator which consisted of a U tube containing a little water, at the most enough to form a column in the tube 2″ high. The gas was passed at such a rate that streams of bubbles issued from the small holes of the inlet tube, and that a few bubbles came through the water in the U tube. When the air in the absorber had been displaced, the tap was turned off, and the vessel shaken vigorously for about 5 minutes. Then it was allowed to stand for 10 minutes, after which the shaking was repeated, the gas being able to enter freely through the inlet tube all the time. The tap of the absorber was not opened after the air had been displaced at the beginning; if it were, air was apt to enter, and to lower the sulphur dioxide content of the acid. After 1—2 hours no bubbles rose from the inlet tube when the vessel was shaken. Saturation was then complete.

Analysis.—Samples were taken for analysis in "oleum bulbs" (Fig. 1*c*) by inserting the capillary of a bulb through the open tap and sucking up about 2 g. of oleum. The capillary was sealed in a flame, and a rubber plug was inserted in the suction tube of the sampling bulb to prevent the escape of dioxide. After being weighed, the bulb was placed, capillary downwards, in a glass bottle containing either 25 or 50 c.c. of N/10-iodine solution and 300—400 c.c. of water, and the bulb was then broken by shaking. The closed bottle and its contents were allowed to stand until the fume had settled. When the stopper of the bottle was removed, the remains of the bulb were thoroughly broken with a glass rod. The excess of unreduced iodine was then titrated with N/10-thiosulphate solution in the usual way, and the total acidity was found by titrating with N-sodium hydroxide solution with methyl-red as indicator. From the result of this titration, to determine the acidity due to the sulphuric acid or sulphur trioxide present before any dioxide was added, an amount equivalent to twice the iodine added must be subtracted in accordance with the equation $SO_2 + H_2O + I_2 = H_2SO_4 + 2HI$.

This method of analysis was tested in several ways. (1) It was first shown that no trioxide was lost when bulbs filled with oleum were broken under water or under iodine solution. Estimations of the same oleum gave 83·33, 83·39% of SO_3 when the bulb was broken under water containing sodium hydroxide, 83·43, 83·45% under water alone, and 83·3% under water containing 25 c.c. of N/10-iodine solution. (2) The iodine titration is not affected by the presence of sulphuric acid. A solution of sodium metabisulphite was made, and measured volumes were titrated with iodine and thiosulphate with and without the amount of sulphuric acid to be expected: no difference could be found. (3) The sampling bulbs were found to lose weight during weighing in the customary way with oleum in them. This was overcome by sealing one end after the bulb had been filled, and putting a rubber stopper into the other. (4) Two samples were taken from the same oleum saturated with sulphur dioxide, one sample by suction, and the other by forcing the oleum into the bulb by applying an air pressure above the oleum in an earlier form of absorption vessel which allowed of this being done. The two samples gave the same result. Suction did not therefore reduce the dioxide content of the liquid.

When gas containing only 6% of sulphur dioxide was used, it was found much harder to reach equilibrium and a more efficient absorber was necessary. Fig. 1(*b*) is a diagram of it. The body contained glass beads supported on a loosely-fitting porous plate. The gas was passed in through the side tube. Just so much acid (about 60 c.c.) was used that the bubbling caused some of it to be carried up into the glass beads. The gas mixture was delivered from an apparatus used to mix sulphur dioxide and air for laboratory catalyst tests. Its dioxide content was within the limits 5·9—6·1%. To avoid the removal of sulphur trioxide from the oleum in the absorber, the gas mixture was passed first through Drechsel bottles containing about 250 c.c. of the same oleum, and standing in the same thermostat. Equilibrium was reached in 4 hours or more. Samples for analysis were drawn into oleum bulbs, the drawn-out stems of the bulb being inserted through the stopcocks as before.

It may be added that the technique of these measurements, of both solubility and of absorption from 6% mixtures, proved difficult, and that numerous determinations were necessary to give confidence in the results.

RESEARCH DEPARTMENT, IMPERIAL CHEMICAL INDUSTRIES LIMITED,
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[*Received, March 21st*, 1946.]

165. *Methylenechloroamine.*

By (Miss) Monica Lindsay and F. G. Soper.

Methylenechloroamine, prepared by the action of monochloroamine on formaldehyde, first isolated by Cross, Bevan, and Bacon, has been shown to be identical with *N*-trichlorotrimethylenetriamine obtained from hexamethylenetetramine and hypochlorite isolated by Delépine. The formation of the trimeric form in solution from monochloroamine and formaldehyde has been followed cryoscopically.

Cross, Bevan, and Bacon (*J.*, 1910, **97**, 2404) prepared methylenechloroamine of empirical formula CH_2NCl by allowing monochloroamine and formaldehyde to react in aqueous solution, obtaining molecular weights of 133, 132·7, and 131·7 [Calc. for $(CH_2NCl)_2$: 127] from f. p. measurements in benzene. Delépine (*Compt. rend.*, 1899, **128**, 108) obtained a compound $(CH_2NCl)_3$ from formaldehyde-ammonia and hypochlorous acid, and later (*Bull. Soc. chim.*, 1911, **9**, 1025) showed that hypochlorite reacts with aqueous solutions of hexamethylenetetramine to form *N*-dichloropentamethylenetetramine, but in the presence of acetic acid gives *N*-trichlorotrimethylenetriamine which has the same composition as Cross, Bevan, and Bacon's compound.

In the present work the compound resulting from monochloroamine and formaldehyde has been further examined. Molecular-weight determinations in benzene and in nitrobenzene using Roberts and Bury's method (*J.*, 1923, **123**, 2040) all gave values *ca.* 190 corresponding to the formula $(CH_2NCl)_3$. The solids prepared (i) by this method and (ii) by the action of hypochlorite on hexamethylenetetramine in the presence of acetic acid decomposed before melting at about 75°. Samples of each were submitted to Dr. F. J. Turner of the Department of Geology, University of Otago, who reported that they were crystallographically identical. The optic axial angle, $2V$, for sample (i) had values 76, 78, 75, 76, 78, 79, and for sample (ii) 73, 82, 76, 78, 80. Optic sign +.

The rate of formation of the methylenechloroamine, $CH_2{:}NCl$, from monochloroamine and formaldehyde and of its polymerisation to the trimeric form have been followed cryoscopically. This is possible since

$$\text{(A)}\ 3NH_2Cl + 3CH_2O = 3CH_2NCl + 3H_2O \qquad \text{(B)}\ 3CH_2NCl = (CH_2NCl)_3$$

reaction (A) in water is attended by a disappearance of 3 solute molecules and reaction (B) by a further disappearance of 2 solute molecules. The initial reaction takes place at temperatures near 0° in under 5 minutes, whereas the polymerisation is complete in about 1 hour, as shown by plotting freezing points of the aqueous mixture of formaldehyde and monochloroamine against time.

Cryoscopic measurements using acetaldehyde were in accord with the view that 1 mol. of chloroamine reacts with 1 mol. of acetaldehyde to form an analogous chloroamine, $CH_3{\cdot}CH{:}NCl$. The freezing point rose slightly above the value for the monomeric compound, indicating some polymerisation, but later fell rapidly, indicating decomposition. The compound isolated from acetaldehyde-ammonia and hypochlorite was similarly unstable, deflagrating when dry (cf. Delépine, *Compt. rend.*, 1897, **125**, 951), and we could not make molecular-weight determinations.

Experimental.

Materials.—Monochloroamine was prepared as in "Inorganic Syntheses," **1**, 59. The solution (0·5M) was stabilised by adding a small quantity of ammonia (0·005N) which caused a negligible depression of the freezing point. The molar concentration given cryoscopically exceeds that of monochloroamine, estimated iodometrically, owing to the presence of ammonium chloride unavoidably formed by the decomposition $3NH_2Cl = NH_4Cl + N_2 + 2HCl$. Formaldehyde was prepared by heating paraformaldehyde in water, and the molar concentration obtained cryoscopically agreed with that obtained by oxidation with hydrogen peroxide in the presence of excess of standard sodium hydroxide and back titration with standard acid.

Methylenechloroamine was prepared for molecular-weight determinations by the method of Cross, Bevan, and Bacon (*loc. cit.*); it separated after approximately 15 minutes in feathery crystals, and, after being dissolved in chloroform and dried, it was deposited in long, shining needles (purity 95—99·5% by titration). When prepared by Delépine's method from hexamine and hypochlorite acidified with acetic acid, the solid was deposited first as feathery crystals and behaved similarly on recrystallisation from chloroform.

Molecular Weights in Benzene and Nitrobenzene.—By using weights of solute, prepared by Cross, Bevan, and Bacon's method, of 0·2—0·46 g. in 22 g. of "AnalaR" benzene, molecular weights of 198, 190, and 180 were obtained [Calc. for $(CH_2NCl)_3$: 190·5]. To determine whether the chloroamine is trimeric under more dissociating conditions, nitrobenzene was used. This solvent has the disadvantage of being hygroscopic, but by using the salt hydrate pair, anhydrous sodium sulphate and decahydrate (2 g. in 20 g. of nitrobenzene), the water content is kept constant (Roberts and Bury, *loc. cit.*). The results obtained by using 0·07—0·58 g. of solute in 20 g. of nitrobenzene were 196·0, 203·0, 182·7, 178·0, 194·5, 194·0, 191·8; mean 191.

Rates of Formation and Polymerisation of Methylenechloroamine.—A 1·0M-solution of formaldehyde or of monochloroamine will depress the f. p. of water by 1·87°. Hence if an aqueous solution is 1·0M with respect to each, the f. p. of the solution should be approximately − 3·74°. As the reaction $NH_2Cl + CH_2O \longrightarrow CH_2NCl + H_2O$ proceeds, the f. p. should rise to − 1·87°, and if the polymerisation $3CH_2NCl \longrightarrow (CH_2NCl)_3$ occurs without separation of solid, the f. p. should rise to − 0·62°. The further rise towards 0° as the trimer crystallises out is limited by its partial solubility, and by the presence of any decomposition products.

In the actual experiment corresponding to the table, the monochloroamine solution containing ammonium chloride as impurity had a f. p. depression of 1·40°. The concentration of the monochloroamine in solution, from its iodine titre, was 0·29M. To 20 c.c. of the monochloroamine solution, 1·20 c.c. of 4·98M-formaldehyde were added, making the concentration of monochloroamine 0·27M and of formaldehyde 0·28M. Thus the solution of monochloroamine (with its accompanying ammonium chloride) has been diluted in the ratio of 20 to 21·2 c.c., giving a depression of 1·32°, which would be increased, if no reaction occurred, by 0·52° by the presence of 0·28M-formaldehyde, giving a total f. p. depression of 1·84°. If the monomeric chloroamine is formed, the depression should clearly decrease to 1·32°, and still further

to 0·98° if the trimeric chloroamine is formed without separation as solid. The freezing points observed are given below.

Time (mins.)	5	10	15	20	25	30	40	50	60	70	77	91	123
ΔT	1·32°	1·27°	1·23°	1·17°	1·12°	1·11°	1·07°	1·04°	1·00°	0·97°	0·94°[1]	0·87°[2]	0·86°

[1] Solution becoming cloudy. [2] White solid separating.

It is clear that the formation of the monomeric form has been completed within 5 minutes, and that the polymerisation continues at the temperature of the experiment over the following hour.

Other runs gave similar curves, but if formaldehyde is in excess a comparatively slow side reaction occurs, as shown by a greater rise than is required for the formation of $(CH_2NCl)_3$. This is due to the formation of hexamethylenetetramine by the reaction $6CH_2O + 4NH_4Cl = C_6H_{12}N_4 + 4HCl + 6H_2O$. This reaction cannot occur appreciably when equimolar amounts of chloroamine and formaldehyde are used, owing to the rapid removal of the formaldehyde as methylenechloroamine.

When the concentration of monochloroamine is in slight molar excess, the polymerisation appears to be slower. When a mixture 0·32M with respect to formaldehyde and 0·37M with respect to monochloroamine was examined, the initial rise of the f. p. corresponded to a disappearance of 0·32 mol. from the solution, *i.e.*, to the formation of monomeric methylenechloroamine. The freezing point stayed approximately constant at this level for about 15 minutes before rising.

The authors' grateful thanks are due to Dr. F. J. Turner for his crystallographic examination of the two specimens of crystals.

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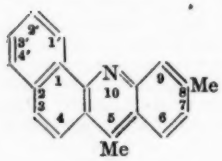
166. *The Chemistry of Carcinogenic Nitrogen Compounds. New Derivatives of the Angular Benzacridines and of Some Related Nuclei.*

By NG. PH. BUU-HOÏ.

In continuation of earlier work on the synthesis of carcinogenic nitrogen compounds (Buu-Hoï and Lecocq, *Compt. rend.*, 1944, **218**, 792), several methyl and halogen *derivatives* of 1 : 2- and 3 : 4-benzacridine have been prepared, by known methods, for examination of their physiological properties. In connexion with the same problem, some homologues of acridine, of 1 : 2 : 5 : 6- and 3 : 4 : 5 : 6-dibenzacridine, and of 1 : 2-benzcarbazole, mostly bearing substituents in the *meso*-position, have also been synthesised.

It has generally been observed that the replacement by nitrogen of a nuclear carbon atom in the molecules of carcinogenic hydrocarbons results in a significant lowering of their physiological activity. As a consequence of those earlier findings, it could hardly be expected that very potent carcinogens would be encountered among the group of polycyclic nitrogen compounds. Recently, however, report has been made of the very high activity displayed by some *meso*-substituted derivatives of 1 : 2-benzacridine (Buu-Hoï, Lacassagne, Lecocq, and Rudali, *Compt. rend. Soc. Biol.*, 1945, **139**, 955). For instance, 5 : 8-dimethyl-1 : 2-benzacridine (I) (Buu-



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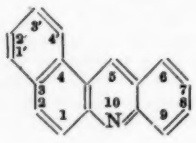
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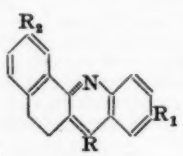

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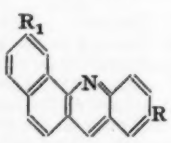


(IV.)

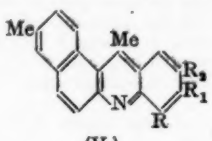
Hoï and Lecocq, *loc. cit.*) develops papilloma and epithelioma on the skin of mice in a proportion and with a rapidity approaching those characteristic of such a prominent carcinogenic hydrocarbon as 20-methylcholanthrene. On the other hand the isomeric 5 : 7- and 5 : 8-dimethyl-3 : 4-benzacridines, though derived from a similar ring system (II), are not active, or only very feebly so. These striking results make desirable a thorough investigation of the whole field of acridine derivatives. The present paper deals with the preparation and properties of some benzacridines of types (I) and (II), bearing methyl or halogen substituents in various positions.

7-Methyl-1-tetralone reacts with potassium isatate to give *2′-methyl-3 : 4-dihydro-1 : 2-benzacridine-5-carboxylic acid* (III; R = CO_2H, R_1 = H, R_2 = Me) which retains tetrophan activity (cf. von Braun and Wolff, *Ber.*, 1922, **55**, 3685), and readily loses carbon dioxide on vacuum distillation to afford *2′-methyl-3 : 4-dihydro-1 : 2-benzacridine* (III; R = R_1 = H, R_2 = Me); this is converted into *2′-methyl-1 : 2-benzacridine* (IV; R = H, R_1 = Me) by heating either with chloranil in xylene solution (cf. Arnold and Collins, *J. Amer. Chem. Soc.*, 1939, **61**, 140; 1940, **62**, 983) or with lead monoxide at 300—320°. The aforementioned tetralone, condensed with potassium 5-bromoisatate, gives *7-bromo-2′-methyl-3 : 4-dihydro-1 : 2-benzacridine-5-carboxylic acid* (III; R = CO_2H, R_1 = Br, R_2 = Me), the decarboxylation product of which, *7-bromo-2′-methyl-3 : 4-dihydro-1 : 2-benzacridine* (III; R = H, R_1 = Br, R_2 = Me), loses bromine when heated with lead monoxide at high temperatures (cf. von Braun and Wolff, *loc. cit.*), but may undergo oxidation into *7-bromo-2′-methyl-1 : 2-benzacridine* (IV; R = Br, R_1 = Me) on treatment either with bromine or better with chloranil in boiling

amene. The same condensation, performed with potassium 5-chloroisatate, leads to chlorine *analogues*, the acid also showing some tetrophan activity.

Cyclodehydrogenation of *N-as.-m*-xylyl-α-naphthylamine (Buu-Hoï and Lecocq, *Compt. rend.*, 1944, **218**, 648, 792) occurs on heating this base with lead monoxide at 320—350° (cf. Ullmann and La Torre, *Ber.*, 1906, **37**, 2924), the resulting *7-methyl*-1 : 2-*benzacridine* (IV; R = Me, R_1 = H) being also obtained *via* the atophan-like *7-methyl*-3 : 4-*dihydro*-1 : 2-*benzacridine*-5-*carboxylic acid* (III; R = CO_2H, R_1 = Me, R_2 = H) and the 7-*methyl*-3 : 4-*dihydro*-1 : 2-*benzacridine* (III; R = R_2 = H, R_1 = Me) through a Pfitzinger synthesis involving α-tetralone and potassium 5-methylisatate. None of these 1 : 2-benzacridines has been found to be carcinogenic (private communication from Prof. Lacassagne).

The modified Bernthsen reaction (cf. Buu-Hoï and Lecocq, *loc. cit.*) performed with *N-o*-tolyl-6-methyl-2-naphthylamine (Buu-Hoï, Hiong-Ki-Wei, and Royer, *Bull. Soc. chim.*, 1945, **12**, 904), acetic anhydride, and zinc chloride gives 2′ : 5 : 9-*trimethyl*-3 : 4-*benzacridine* (V; R = Me, R_1 = R_2 = H) in rather poor yield. Using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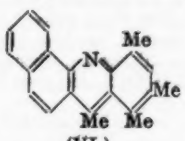
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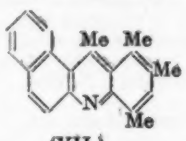
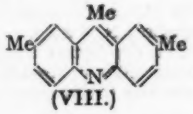

(VII.)

N-m-tolyl- and *N-p*-tolyl-6-methyl-2-naphthylamine, 2′ : 5 : 8- (V; R = R_2 = H, R_1 = Me) and 2′ : 5 : 7-*trimethyl*-3 : 4-*benzacridine* (V; R = R_1 = H, R_2 = Me) are respectively obtained. 5 : 6 : 7 : 9-Tetramethyl-1 : 2- (VI) and -3 : 4-benzacridine (VII) were prepared in the same manner from *N*-ψ-cumyl-α- and -β-naphthylamine (Buu-Hoï and Lecocq, *loc. cit.*) respectively. Both are slowly active in the production of epithelioma. The *picrate* of (VI) melts considerably lower than that of (VII); this is consistent with a similar observation made by Senier and Austin (*J.*, 1907, **91**, 1240) regarding the picrates from 5 : 6 : 8-trimethyl-1 : 2- and -3 : 4-benzacridines.

The Bernthsen reaction may also be applied to the synthesis of halogenated *meso*-substituted benzacridines: thus, 8-*chloro*-5-*methyl*-3 : 4-*benzacridine* was obtained from *N-m*-chlorophenyl-β-naphthylamine, and the isomeric 9-*chloro*-compound from *N-o*-chlorophenyl-β-naphthylamine.

In view of the activity of some *meso*-substituted anthracenes, recently reported by several authors (Kennaway and Warren, 1941), 3 : 5 : 7-*trimethylacridine* (VIII) has now been prepared for examination, using di-*p*-tolylamine, acetic anhydride, and zinc chloride. The same route was found suitable for the preparation of 5-*methyl*-3 : 4 : 6 : 7-*dibenzacridine* (IX) from ββ-dinaphthylamine. An analogue of the feebly carcinogenic 3′-methyl-1 : 2 : 5 : 6-dibenzanthracene (Cook, *J.*, 1931, 489), 3′-*methyl*-1 : 2 : 6 : 7-*dibenzacridine* (X), was readily obtained on heating 6-methyl-2-naphthol (Dziewoński, Schoenówna, and Waldmann, *Ber.*, 1925, **58**, 1912) with α-naphthylamine and trioxymethylene, following the Ullmann–Fettvadjian procedure for the preparation of the non-methylated dibenzacridine (*Ber.*, 1903, **36**, 1029).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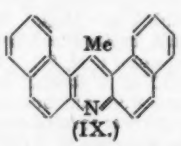
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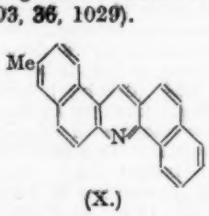
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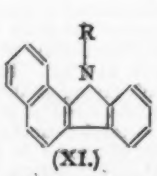
(XI.)

Since 1 : 2-benzcarbazole (XI; R = H) has been claimed (Schürch and Winterstein, *Z. physiol. Chem.*, 1935, **136**, 79) to produce epithelial growths, a series of N-*alkyl*-1 : 2-*benzcarbazoles* (XI) were synthesised by allowing various alkyl halides to react with the sodio-derivative of 1 : 2-benzcarbazole. None of them appears to be actively carcinogenic, thus indicating that *meso*-substitution is effective only in an aromatic ring.

Some of the new substances described in this paper are being examined for anticarcinogenic activity (cf. Lacassagne, Buu-Hoï, and Rudali, *Brit. J. Exp. Path.*, 1945, **26**, 5); the biological data will be published elsewhere. Some methyl derivatives of 3 : 4-benzacridine have been used with success for inhibition of tumour-growth by Badger *et al.* (*Proc. Roy. Soc.*, 1942, *B*, **130**, 265).

This investigation will be continued.

Experimental.

2′-*Methyl*-1 : 2-*benzacridine*.—A mixture of isatin (1·5 g.), 7-methyl-1-tetralone in slight excess (1·7 g.), and potassium hydroxide (1·7 g. in 15 c.c. of 70% ethyl alcohol) was gently boiled for 12 hours on the water-bath. The slightly brown solution was diluted with water (50 c.c.), and twice shaken with ether in order to remove traces of unreacted ketone. On acidification with a slight excess of 50% acetic acid, the aqueous solution gave 2′-*methyl*-3 : 4-*dihydro*-1 : 2-*benzacridine*-5-*carboxylic acid* (2·5 g.), which crystallised from nitrobenzene in yellowish silky needles, m. p. 276° (efferv.) (Found: N, 4·6; $C_{19}H_{15}O_2N$ requires N, 4·8%). This (2·0 g.) was fused, and the residue subsequently distilled in a vacuum. The distillate was moistened with alcohol and kept overnight; 2′-*methyl*-3 : 4-*dihydro*-1 : 2-*benzacridine* then separated as long colourless needles (1 g.), m. p. 103—104°, readily soluble in benzene, sparingly in alcohol (Found: N, 5·4. $C_{18}H_{15}N$ requires N, 5·7%). This base develops on heating a smell resembling that of tobacco; the alcoholic solutions exhibit a strong blue fluorescence; sulphuric solutions are greenish-yellow. The *picrate* crystallised from nitrobenzene in fine yellow needles, m. p. 218—219° (decomp.), which were almost insoluble in alcohol (Found: N, 12·4. $C_{18}H_{15}N,C_6H_3O_7N_3$

requires N, 12·6%). The dihydro-base (1 g.) was heated during ½ hour at 300—320° with excess of lead monoxide (50 g.); the cooled mass was extracted twice with boiling alcohol, and the alcoholic extract boiled with charcoal and evaporated to small bulk. *2′-Methyl-1 : 2-benzacridine* separated on cooling in long, glittering, yellowish needles, m. p. 125°, which were readily soluble in benzene, sparingly in alcohol (Found: N, 5·5. $C_{18}H_{13}N$ requires N, 5·7%). The orange-yellow *picrate* crystallised from nitrobenzene in fine prismatic needles, m. p. 236—237° (decomp.) (Found: N, 12·5. $C_{18}H_{13}N,C_6H_3O_7N_3$ requires N, 12·7%).

7-Bromo-2′-methyl-1 : 2-benzacridine.—5-Bromoisatin (2·3 g.), condensed with 7-methyl-1-tetralone (1·8 g.) in the presence of alcoholic potassium hydroxide (1·7 g.) during 12 hours, gave almost quantitatively *7-bromo-2′-methyl-3 : 4-dihydro-1 : 2-benzacridine-5-carboxylic acid* (4 g.), which crystallised from acetic acid in silky yellowish needles, m. p. 239—240° (decomp.) (Found: N, 3·7. $C_{19}H_{14}O_2NBr$ requires N, 3·9%). This acid strongly retains solvent, which it loses above 160°. Decarboxylation gave a viscous resin which did not solidify spontaneously, and was therefore converted into a *picrate* (4 g.) which crystallised from nitrobenzene in silky yellow needles, m. p. 241—242° (decomp.) (Found: N, 10·2. $C_{18}H_{14}NBr,C_6H_3O_7N_3$ requires N, 10·1%). *7-Bromo-2′-methyl-3 : 4-dihydro-1 : 2-benzacridine*, regenerated from this picrate by treatment with aqueous ammonia, gave long colourless needles, m. p. 98—99°, on recrystallisation from alcohol (Found: N, 4·2. $C_{18}H_{14}NBr$ requires N, 4·3%). A solution of this dihydro-base in boiling cumene was treated dropwise with excess of bromine, heating being continued until evolution of hydrogen bromide had ceased. The orange-yellow precipitate was collected, washed with ether, and decomposed by aqueous ammonia. *7-Bromo-2′-methyl-1 : 2-benzacridine* formed clumps of yellowish needles (1·8 g.) from alcohol (Found: N, 4·2. $C_{18}H_{12}NBr$ requires N, 4·4%); its *picrate*, which formed silky, glistening, orange needles from nitrobenzene, darkened and charred above 228—230° (Found: N, 10·1. $C_{18}H_{12}NBr,C_6H_3O_7N_3$ requires N, 10·2%). The base regenerated from the picrate had m. p. 108°.

7-Chloro-2′-methyl-3 : 4-dihydro-1 : 2-benzacridine.—5-Chloroisatin (3 g.), 7-methyl-1-tetralone (3 g.), and potassium hydroxide (3 g.) yielded *7-chloro-2′-methyl-3 : 4-dihydro-1 : 2-benzacridine-5-carboxylic acid* (4·8 g.) as faintly yellowish needle rosettes, m. p. 230—231° (from alcohol) (Found: N, 4·2. $C_{19}H_{14}O_2NCl$ requires N, 4·3%). The corresponding *7-chloro-5′-methyl-3 : 4-dihydro-1 : 2-benzacridine* formed long silky yellowish needles (from alcohol) (Found: N, 5·2. $C_{18}H_{14}NCl$ requires N, 5·0%), and gave a *picrate* which crystallised from nitrobenzene in flimsy orange-yellow needles, m. p. 229—230° (decomp.) (Found: N, 10·8. $C_{18}H_{14}NCl,C_6H_3O_7N_3$ requires N, 11·1%).

7-Methyl-1 : 2-benzacridine.—(a) *Ullmann and La Torre's reaction. N-as.-m-Xylyl-β-naphthylamine* (3 g.) was heated at 325° in a metal-bath for ½ hour; the temperature was then raised until distillation occurred, and the thick jelly thus obtained was treated with excess of an alcoholic solution of picric acid. After recrystallisation from nitrobenzene, the *picrate* formed yellow needles, m. p. 226—227°, insoluble in cold alcohol, slightly soluble in benzene (Found: N, 12·3. $C_{18}H_{13}N,C_6H_3O_7N_3$ requires N, 12·7%). The free *base*, liberated from the picrate by treatment with aqueous ammonia, separated from alcohol in long almost colourless prismatic needles, m. p. 131° (Found: N, 5·4. $C_{18}H_{13}N$ requires N, 5·7%). The hydrochloride formed silky yellow needles from water, and gave solutions showing an intense green fluorescence.

(b) *Pfitzinger's reaction.* 5-Methylisatin (2·8 g.) was allowed to react with α-tetralone (2·8 g.) in the presence of potassium hydroxide (3 g.) in alcohol (25 c.c.), thus giving *7-methyl-3 : 4-dihydro-1 : 2-benzacridine-5-carboxylic acid* (4·8 g.), which crystallised from alcohol in almost colourless needles, m. p. 286—288° (Found: N, 4·7. $C_{19}H_{15}O_2N$ requires N, 4·8%). Decarboxylation gave *7-methyl-3 : 4-dihydro-1 : 2-benzacridine*, which separated from alcohol in colourless silky needles, m. p. 72°, very soluble in hot alcohol and benzene (Found: N, 5·5. $C_{18}H_{15}N$ requires N, 5·7%). This dihydro-base gave a *picrate* crystallising from much alcohol in yellow prisms, m. p. 211—212° (Found: N, 12·4. $C_{18}H_{15}N,C_6H_3O_7N_3$ requires N, 12·7%), and was easily converted into 7-methyl-1 : 2-benzacridine (m. p. 127—128° after two recrystallisations from alcohol) by heating with lead monoxide at 300—320°. The same oxidation took place when a solution of the dihydro-base in cumene was boiled during 6 hours with a slight excess of chloranil.

2 : 5 : 9-Trimethyl-3 : 4-benzacridine.—*N-o-*Tolyl-6-methyl-2-naphthylamine (2 g.) was heated with freshly fused zinc chloride (2 g.) and acetic anhydride (6 c.c.) during 18 hours at 190—200° (extensive charring occurred above 200°). The sticky greenish fluorescent mass thus obtained was treated with a hot 40% aqueous solution of potassium hydroxide in the presence of benzene; the benzene layer was decanted and dried (Na_2SO_4). After removal of the solvent and vacuum distillation of the thick brown residue, the crude benzacridine was converted into its *picrate* (1 g.); silky yellow needles (from nitrobenzene), m. p. 223—224° (decomp.), almost insoluble in alcohol (Found: N, 10·9. $C_{20}H_{17}N,C_6H_3O_7N_3$ requires N, 11·2%). The *base* (0·6 g.), freed by aqueous ammonia, crystallised from alcohol in almost colourless needles, m. p. 118°, giving an intense yellow colour with sulphuric acid (Found: N, 5·1. $C_{20}H_{17}N$ requires N, 5·2%).

2′ : 5 : 8-Trimethyl-3 : 4-benzacridine.—This *base* was obtained in a similar manner, but in far better yield (1 g.), from *N-m-*tolyl-6-methyl-2-naphthylamine (2 g.). It crystallised from alcohol–benzene in long silky yellowish needles, m. p. 198° (Found: N, 5·2. $C_{20}H_{17}N$ requires N, 5·2%). The *picrate* formed yellow silky needles (from nitrobenzene), m. p. 261—262° (efferv.) (Found: N, 11·4. $C_{20}H_{17}N,C_6H_3O_7N_3$ requires N, 11·2%).

2′ : 5 : 7-Trimethyl-3 : 4-benzacridine.—This *base* formed very slightly yellowish needles (from alcohol), m. p. 135—136°, readily soluble in ether (Found: N, 5·1. $C_{20}H_{17}N$ requires N, 5·2%). The *picrate* formed short yellow prisms (from nitrobenzene), m. p. 243—244° (efferv.) (Found: N, 10·8. $C_{20}H_{17}N,C_6H_3O_7N_3$ requires N, 11·2%).

5 : 6 : 7 : 9-Tetramethyl-3 : 4-benzacridine.—From *N-ψ-*cumyl-β-naphthylamine (4 g.), zinc chloride (4 g.), and acetic anhydride 10 c.c., heated for 12 hours at 200—220°), the crude *base* (2·8 g.) was obtained. This spontaneously solidified after distillation (b. p. 272—275°/18 mm.), and crystallised from alcohol in faintly yellowish prismatic needles, m. p. 189—190°, extremely soluble in benzene, slightly in alcohol or acetone (Found: N, 5·1. $C_{21}H_{19}N$ requires N, 4·9%). The hydrochloride formed deep yellow needles, very sparingly soluble in water; the *picrate* crystallised from nitrobenzene in short glistening orange prisms, m. p. 252—253° (Found: N, 10·7. $C_{21}H_{19}N,C_6H_3O_7N_3$ requires N, 10·9%).

5 : 6 : 7 : 9-Tetramethyl-1 : 2-benzacridine.—This base was still more soluble in benzene than the previous isomer; it formed faintly yellowish needles, m. p. 154° (from alcohol), and gave a *picrate* crystallising from benzene in elongated orange-yellow prisms, m. p. 169—170°, easily soluble in alcohol and benzene (Found: N, 5·0. $C_{21}H_{19}N$ requires N, 4·9%).

7-Chloro-5-methyl-3 : 4-benzacridine.—*N-m-*Chlorophenyl-β-naphthylamine (Knoevenagel, *J. pr. Chem.*, 1914, **89**, 17) (2 g.) was heated with zinc chloride (3 g.) and acetic anhydride (6 c.c.) during 24 hours at 220—230°. The *base* thus obtained could be distilled in a high vacuum without decomposition, and crystallised from benzene in long, prismatic, almost colourless needles, m. p. 183°, which were very sparingly soluble in alcohol (Found: N, 5·1. $C_{18}H_{12}NCl$ requires N, 5·0%). The *picrate* formed deep yellow needles, m. p. 197°, from nitrobenzene (Found: N, 11·0. $C_{18}H_{12}NCl,C_6H_3O_7N_3$ requires N, 11·2%).

9-Chloro-5-methyl-3 : 4-benzacridine.—After two recrystallisations from alcohol–benzene, this *base* formed yellowish silky needles, m. p. 129° (Found: N, 5·3. $C_{18}H_{12}NCl$ requires N, 5·0%). It gave a *picrate* which crystallised from nitrobenzene in short yellow prisms which decomposed above 216—217° (Found: N, 11·4. $C_{18}H_{12}NCl,C_6H_3O_7N_3$ requires N, 11·2%).

3 : 5 : 7-Trimethylacridine.—Di-*p-*tolylamine (5 g.) was heated with zinc chloride (7 g.) and acetic anhydride (5 c.c.)

during 18 hours at 230—250°; the *base* (3 g.) was conveniently purified by distillation in a high vacuum (b. p. 195°/2·5 mm.); it separated from aqueous acetone in feebly yellowish silky needles, m. p. 84°, extremely soluble in alcohol and benzene (Found: N, 6·4. $C_{16}H_{15}N$ requires N, 6·3%). The *picrate* formed glistening yellow needles, m. p. 219—220° (from nitrobenzene) (Found: N, 12·3. $C_{16}H_{15}N,C_6H_3O_7N_3$ requires N, 12·4%).

3'-Methyl-1 : 2 : 6 : 7-dibenzacridine.—A mixture of 6-methyl-2-naphthol (2 g.) and α-naphthylamine (2 g.) was fused at 160—170° and carefully treated with paraformaldehyde (0·4 g.); a violent reaction took place with evolution of steam and considerable frothing. The temperature was subsequently raised to 260°, and the reaction product vacuum distilled; after two recrystallisations from benzene, the *acridine* (3·2 g.) was obtained as silky yellowish needles, m. p. 195°, very sparingly soluble in alcohol (Found: N, 4·9. $C_{22}H_{15}N$ requires N, 4·7%). The *picrate* crystallised from nitrobenzene in orange-yellow needles which decomposed above 250° (Found: N, 10·4. $C_{22}H_{15}N,C_6H_3O_7N_3$ requires N, 10·7%).

5-Methyl-3 : 4 : 6 : 7-dibenzacridine.—Knoevenagel (*loc. cit.*) claimed that he had obtained pure ββ-dinaphthylamine by heating a solution of β-naphthylamine in aniline with traces of iodine. However, when a sample thus prepared was submitted to a Bernthsen synthesis with acetic anhydride and zinc chloride, 5-methyl-3 : 4-benzacridine (Posstowski and Lundin, *Centr.*, 1940, II, 205) (almost colourless silky needles, b. p. 250°/2 mm., m. p. 144°) was isolated from the reaction mixture; the picrate of this base had m. p. 237° after recrystallisation from nitrobenzene. Hence, it is clear that Knoevenagel's ββ-dinaphthylamine was contaminated by *N*-phenyl-β-naphthylamine. A purer product was obtained by heating β-naphthol with β-naphthylamine in the presence of iodine; by Bernthsen's reaction this yielded only *5-methyl-3 : 4 : 5 : 6-dibenzacridine* (IX), which distilled above 300°/2 mm. and formed straw-coloured silky needles, m. p. 184—185° after repeated crystallisation from alcohol–benzene (Found: N, 4·5. $C_{22}H_{15}N$ requires N, 4·7%). The benzene solutions showed a strong violet fluorescence and the sulphuric solutions were intensely yellow. The picrate formed silky yellow-orange needles (from nitrobenzene) which decomposed above 278—280°.

N-Alkyl-1 : 2-benzcarbazoles.—These were prepared by the following procedure: a solution of 1 : 2-benzcarbazole in dry toluene or xylene (Bucherer and Sonnenburg, *J. pr. Chem.*, 1910, **81**, 3, 18) was heated under reflux with a slight excess of finely powdered sodamide until evolution of ammonia had ceased. After cooling, a large excess of an alkyl halide (2 mols.) was added, and the mixture heated again for 2 or 3 hours. The product was poured into iced water, and the toluene (or xylene) layer was collected, washed with water, and dried (Na_2SO_4). After removal of the solvent, the solid residue was crystallised several times from alcohol–benzene (yield, 40—60%). As a rule, the *N*-alkyl-1 : 2-benzcarbazoles were much more soluble in benzene than the non-alkylated product, and like the latter, gave with sulphuric acid a yellow coloration which rapidly became greenish-blue by oxidation in air. The deep red picrates and 1 : 3 : 5-trinitrobenzene complexes were very sparingly soluble in alcohol. The new *compounds* are listed below:

				N, %.	
1 : 2-Benzcarbazoles.	Crystal form.	M. p.	Formula.	Found.	Required.
N-Methyl	Yellowish glinting prisms	168°	$C_{17}H_{13}N$	5·8	6·0
N-Ethyl	Long needles	146	$C_{18}H_{15}N$	5·4	5·7
N-Propyl	Glistening plates	90	$C_{19}H_{17}N$	5·3	5·4
Picrates.					
N-Methyl	Brown-red silky needles	162			
N-Ethyl	Deep reddish-brown prisms	135			
N-Propyl	Short brown needles	106			
1 : 3 : 5-Trinitrobenzene complexes.					
1 : 2-Benzcarbazole	Blood-red needles	190			
N-Methyl	Clumps of red silky needles	187			
N-Ethyl	Vermilion-red needles	157			
N-Propyl	Long silky needles	125			

The author expresses his thanks to Professor Baranger for his keen interest in this work, and to Dr. Hiong-ki-Wei for assistance with the experimental work. Some of the analyses were made by Mr. Mudry.

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167. *The Effect of Steric Hindrance on the Course of Pfitzinger Reactions.*

By NG. PH. BUU-HOÏ.

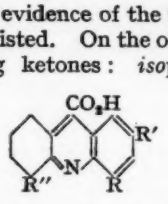
The Pfitzinger reactions between ketones, $R{\cdot}CH_2{\cdot}CO{\cdot}R'$, and various isatins have been shown to be subject to steric hindrance. On the other hand, it has been demonstrated that these condensations are not affected by choosing large molecules as reactants. In the course of the investigation, the hitherto unknown 10-propionyl-3 : 4-benzpyrene has readily been prepared, and its constitution determined.

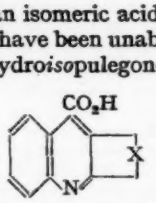
ALTHOUGH the condensation of isatin with ketones, $R{\cdot}CH_2{\cdot}CO{\cdot}R'$, has frequently been used for the synthesis of quinoline derivatives, attention has been paid to neither the steric nor the electronic factors likely to govern the reaction. Some previous isolated observations are consistent with the belief that steric hindrance may interfere with Pfitzinger's reaction. Borsche and Rottsieper (*Annalen*, 1910, **377**, 70) could not bring isatin into reaction with menthone, pulegone, or camphor, and von Braun (*Annalen*, 1927, **451**, 1) observed that tetrahydro-α-naphthisatin failed to react with α-tetralone. These authors, however, have not attempted to account for these remarkable failures.

The present paper forms part of a systematic investigation on the influence of various substituents upon the behaviour of ketones, $R{\cdot}CH_2{\cdot}CO{\cdot}R'$, towards isatin and its derivatives.

(a) *Steric Hindrance in the Ketonic Molecule.*—Isatin gave with 2-methyl*cyclo*hexanone the expected *1-methyl-1 : 2 : 3 : 4-tetrahydroacridine-5-carboxylic acid* (I; R = R' = H; R'' = Me) in very high yield, and *2 : 3-meso**methyltrimethylenecinchoninic acid* (II) was similarly prepared from 3-methyl*cyclo*pentanone. In the

latter reaction, no evidence of the formation of an isomeric acid could be observed, as would be the case if no steric hindrance existed. On the other hand, we have been unable to detect any normal reaction between isatin and the following ketones: *iso*pulegone, dihydro*iso*pulegone, tetrahydrocarvone, and norcamphor. In

(I.) 

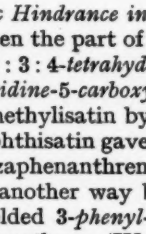


(II; X = CH_2·CHMe·CH_2)
(III; X = $[CH_2]_{12}$)

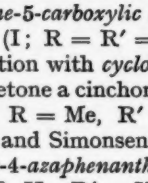
addition to menthone and camphor previously mentioned (Borsche *et al., loc. cit.*), all these ketones bear substituents near both the carbonyl and the methylene group which would be involved in Pfitzinger's condensation. This conforms with the inability, already recorded by Borsche (*Ber.*, **1924**, **57**, 1373), of dehydrocholic and dehydrodeoxycholic acid (as well as some other analogous derivatives of bile constituents) to react with more than one molecule of isatin. The suggested rule may perhaps be of value in the future for the elucidation of the configuration of natural products. **2 : 3-*Tridecamethylenecinchoninic acid*** (III) has been obtained in almost theoretical yield from isatin and *cyclo*pentadecanone, thus indicating that an internal steric hindrance supposed by Angeli (*Gazzetta*, **1930**, **60**, 939) to occur in the molecules of musk-smelling cyclanones does not apparently exist.

(b) *Steric Hindrance in the Isatin Molecule.*—The following examples show that the condensation proceeds normally when the part of the ketonic molecule involved in the reaction is not itself sterically hindered: **7 : 9-*dichloro*-1 : 2 : 3 : 4-*tetrahydroacridine*-5-*carboxylic acid*** (I; R = R′ = Cl, R″ = H) and **7 : 9-*dimethyl*-1 : 2 : 3 : 4-*tetrahydroacridine*-5-*carboxylic acid*** (I; R = R′ = Me, R″ = H) have readily been obtained from 5 : 7-dichloro- and 5 : 7-dimethylisatin by interaction with *cyclo*hexanone.

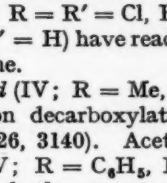
α-Acenaphthisatin gave with acetone a cinchoninic ***acid*** (IV; R = Me, R′ = CO_2H) which yielded **3-methyl-8 : 9-ace-4-azaphenanthrene** (IV; R = Me, R′ = H) on decarboxylation. The last substance had been obtained in another way by Nair and Simonsen (*J.*, **1926**, 3140). Acetophenone and 2-acetylphenanthrene similarly yielded **3-*phenyl*-8 : 9-*ace*-4-*azaphenanthrene*** (IV; R = C_6H_5, R′ = H) and **3-(2′-*phenanthryl*)-8 : 9-*ace*-4-*azaphenanthrene*** (IV; R = $C_{14}H_9$, R′ = H) through the corresponding cinchoninic ***acids*** (IV; R′ = CO_2H).

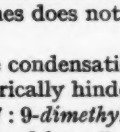


(IV.)



(V.)



(VI; X = CO·Et)
(VII; X = )

(c) *Steric Hindrance in the Molecules of Both Partners.*—In this case, the reaction either fails, or takes an abnormal course: α- and β-Naphthisatins do not react with *cyclo*hexanone (Borsche and Wagner-Roemmich, *Annalen*, 1940, **544**, 274; Robinson and Bogert, *J. Org. Chem.*, **1936**, **1**, 65). We have now found that α-acenaphthisatin follows that rule; furthermore, β-naphthisatin gives with methyl ethyl ketone 2-ethyl-1-azaphenanthrene-4-carboxylic acid (V), whereas isatin is known to afford under the same conditions 2 : 3-dimethylcinchoninic acid as the sole product (Pfitzinger, *J. pr. Chem.*, **1897**, **56**, 283).

A significant proof of the ability of ketones of high molecular weight to react with isatin is provided by the synthesis of **2-(3′ : 4′-*benzpyrenyl*-10′)-3-*methylcinchoninic acid*** (VII) from isatin and **10-*propionyl*-3 : 4-*benzpyrene*** (VI). The last substance has readily been prepared from 3 : 4-benzpyrene, following a procedure devised by Windaus and Raichle (*Annalen*, **1939**, **537**, 157) for the synthesis of the lower homologue; the constitution of (VI) has been ascertained by its conversion into 3 : 4-benzpyrene-10-carboxylic acid on oxidation by sodium hypobromite.

Some of the new substances recorded in this paper are being examined for carcinogenic activity.

Experimental.

1-*Methyl*-1 : 2 : 3 : 4-*tetrahydroacridine*-5-*carboxylic Acid.*—A solution of isatin (10 g.), 2-methyl*cyclo*hexanone (15 g.), and potassium hydroxide (10 g.) in 50% ethanol (100 c.c.) was refluxed during 24 hours on a water-bath. The dark solution obtained was evaporated to half its bulk, twice shaken with ether in order to remove traces of methyl*cyclo*hexanone and other neutral products, and acidified with a slight excess of 50% acetic acid. The *acid* (10 g.) which separated on cooling was twice recrystallised from dilute alcohol, and then formed silky colourless needles, m. p. 267° (efferv.), almost insoluble in benzene, readily soluble in ethanol (Found: N, 6·0. $C_{15}H_{15}O_2N$ requires N, 5·8%).

2 : 3-meso*Methyltrimethylenecinchoninic Acid.*—Isatin (10 g.) and 3-methyl*cyclo*pentanone (20 c.c.) were treated as above with a solution of potassium hydroxide (10 g.) in 50% ethanol (100 c.c.). After acidification with acetic acid, a yellowish precipitate (11 g.) was formed; recrystallisation from benzene–alcohol afforded almost colourless needles of the *acid*, m. p. 277—278° (efferv.) (Found: N, 6·2. $C_{14}H_{13}O_2N$ requires N, 6·1%).

Attempts to Condense Isatin with Some Terpenic Ketones.—No appreciable reaction could be detected between isatin (10 g.) and *iso*pulegone, dihydro*iso*pulegone, tetrahydrocarvone, or norcamphor (15 g.) in the presence of potassium hydroxide (10 g. in 100 c.c. of 50% ethanol), even after 3 days' heating on a water-bath. No definite condensation product could also be obtained with the nitrogen-containing bicyclic ketone, tropanone; these failures cannot be attributed to decomposition of the ketones in the alkaline medium, as they could be recovered largely unchanged by extraction with ether.

2 : 3-*Tridecamethylenecinchoninic Acid.*—This *acid* was obtained in 90% yield when *cyclo*pentadecanone was allowed to react with isatin and potassium hydroxide in the usual manner. It crystallised from alcohol in fine glinting needles, m. p. 297—298° (efferv.), which were very soluble in acetic acid, and gave a tallowy base on decarboxylation (Found : N, 3·5. $C_{22}H_{31}O_2N$ requires N, 3·8%). No frothing occurred when aqueous solutions of its alkali salts were shaken.

7 : 9-*Dichloro*-1 : 2 : 3 : 4-*tetrahydroacridine*-5-*carboxylic Acid.*—5 : 7-Dichloroisatin (7·5 g.) was treated with *cyclo*hexanone (10 g.) and potassium hydroxide (10 g.) in aqueous ethanol (80 c.c.) during 24 hours. The *acid* thus obtained crystallised from *iso*propanol in glistening colourless needles (12 g.), m. p. 302—303° (efferv.), which were almost insoluble in cold ethanol or benzene (Found : N, 4·6. $C_{14}H_{11}O_2NCl_2$ requires N, 4·7%).

7 : 9-*Dimethyl*-1 : 2 : 3 : 4-*tetrahydroacridine*-5-*carboxylic Acid.*—This *acid*, obtained from 5 : 7-dimethylisatin (5 g.) and *cyclo*hexanone (10 g.), formed silky colourless needles, m. p. 247—248° (11 g.), which were fairly soluble in alcohol (Found : N, 5·7. $C_{16}H_{17}O_2N$ requires N, 5·5%). The high yields recorded in this and the foregoing experiment indicate that the amino-groups of both isatins are not sterically hindered.

3-*Methyl*-8 : 9-*ace*-4-*azaphenanthrene*-1-*carboxylic Acid.*—A solution of α-acenaphthisatin (2·2 g.; cf. Langenbeck, Hellrung, and Jüttemann, *Annalen*, 1934, **512**, 276; Buu-Hoï and Hiong-Ki-Wei, *Rev. sci.*, 1944, **82**, 168), acetone (3 c.c.), and potassium hydroxide (3 g.) in aqueous ethanol (30 c.c. of ethanol, 3 c.c. of water) was refluxed during 30 hours on a water-bath. The *acid* thus obtained (2·1 g.) crystallised from alcohol in slender yellowish prisms, m. p. 302° (efferv.) (Found : N, 5·1. $C_{17}H_{13}O_2N$ requires N, 5·0%). It afforded, on decarboxylation and subsequent vacuum-distillation, 3-methyl-8 : 9-ace-4-azaphenanthrene, m. p. 130—131° (Nair and Simonsen, *loc. cit.*, give m. p. 131°). The *hydrochloride* of this base crystallised from dilute hydrochloric acid in long silky bright yellow needles (Found : N, 5·5. $C_{16}H_{13}N,HCl$ requires N, 5·5%).

3-*Phenyl*-8 : 9-*ace*-4-*azaphenanthrene.*—3-*Phenyl*-8 : 9-*ace*-4-*azaphenanthrene*-1-*carboxylic acid* was obtained in 85% yield from α-acenaphthisatin and acetophenone; it crystallised from ethanol in slender yellowish prisms, m. p. 278—279° (efferv.) (Found : N, 4·1. $C_{22}H_{15}O_2N$ requires N, 4·3%). Vacuum distillation produced the corresponding *base*, which crystallised from alcohol–benzene in clumps of silky yellowish needles, m. p. 157° (Found : N, 5·2. $C_{21}H_{15}N$ requires N, 5·0%). Concentrated sulphuric acid produced a deep yellow coloration, and the alcoholic solutions displayed an intense greenish-blue fluorescence; treatment with picric acid gave a molecular complex, which separated from alcohol in long, silky, orange-yellow needles, m. p. 154—155° (decomp.).

3-(2′-*Phenanthryl*)-8 : 9-*ace*-4-*azaphenanthrene.*—The corresponding cinchoninic *acid* was obtained in 80% yield from α-acenaphthisatin and 2-acetylphenanthrene (Mosettig and van der Kamp, *J. Amer. Chem. Soc.*, 1930, **52**, 3704). It crystallised from boiling *iso*amyl alcohol as a yellowish microcrystalline powder which decomposed above 310° (Found : N, 3·1. $C_{30}H_{19}O_2N$ requires N, 3·3%). The aqueous solutions of its sparingly soluble salts with alkali metals give a very persistent foam. The corresponding *base* could be distilled without decomposition, and crystallised from benzene in slight yellowish needles, m. p. 248°, which were very sparingly soluble in alcohol; its solutions in concentrated sulphuric acid were deep yellow and showed an intense green fluorescence (Found : N, 3·5. $C_{29}H_{19}N$ requires N, 3·6%). The picrate was very unstable.

2-*Ethyl*-1-*azaphenanthrene*-4-*carboxylic Acid.*—A solution of β-naphthisatin (2 g.), methyl ethyl ketone (2 c.c.), and potassium hydroxide (2·8 g.) in aqueous ethanol (25 c.c. of ethanol, 2 c.c. of water) was refluxed for 24 hours on a water-bath. The standard treatment gave a cinchoninic acid which crystallised from ethanol in almost colourless silky needles, m. p. 292—293° (efferv.). Doebner and Felber (*Ber.*, 1894, **27**, 2021) record m. p. 283° for the acid prepared by heating propaldehyde, β-naphthylamine, and pyruvic acid. Decarboxylation of our acid gave 2-ethyl-1-azaphenanthrene, m. p. 61° (Doebner and Felber gave m. p. 63°); the *picrate* of this base separated from alcohol in fine yellow needles, m. p. 172—173°, which were extremely soluble in benzene and hot alcohol (Found : N, 13·2. $C_{15}H_{13}N,C_6H_3O_7N_3$ requires N, 12·8%). The presence of the ethyl group accounts for the abnormally low m. p. of the picrate.

10-*Propionyl*-3 : 4-*benzpyrene.*—A solution of 3 : 4-benzpyrene (1·5 g.) in carbon disulphide (50 c.c.) was slowly added to an ice-cooled solution of aluminium chloride (1·5 g.) in propionyl chloride (10 g.). A somewhat violent reaction took place, and the mixture obtained was kept at room temperature for two hours and then poured into dilute hydrochloric acid; the sticky brownish semi-solid mass which separated was extracted with chloroform, the organic layer washed with dilute alkali and with water and dried ($MgSO_4$), and the solvent removed. The solid *residue* was crystallised four times from alcohol–benzene, giving short bright yellow needles, m. p. 125—126°, which dissolved in sulphuric acid with an intense violet coloration (Found : C, 89·4; H, 5·0. $C_{23}H_{16}O$ requires C, 89·6; H, 5·2%). The yield in this experiment (1·5 g.) was somewhat higher than that observed by Windaus and Raichle (*loc. cit.*) for acetylbenzpyrene. This is obviously due to the lesser reactivity of propionyl chloride which prevents it from giving a diketonic by-product. The acid obtained from propionylbenzpyrene and an alkaline solution of sodium hypobromite gave a methyl ester, m. p. 178—179° (Windaus and Raichle give m. p. 181° for the methyl ester of 3 : 4-benzpyrene-10-carboxylic acid).

2-(3′ : 4′-*Benzpyrenyl*-10′)-3-*methylcinchoninic Acid* (VII).—A mixture of 10-propionyl-3 : 4-benzpyrene (0·3 g.), isatin (0·15 g.), and potassium hydroxide (0·2 g. in a few drops of water) was heated with ethanol (25 c.c.) during 24 hours. The cooled mixture was twice extracted with hot xylene after dilution with water, and the aqueous layer acidified with acetic acid. The *acid* (0·3 g.) thus precipitated crystallised from nitrobenzene in deep yellow microscopic needles, m. p. 325—326° (efferv.) (Found : N, 3·1. $C_{31}H_{19}O_2N$ requires N, 3·2%). Sulphuric acid produced an intense purple-red coloration, which rapidly became violet.

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168. *Alkyl–Oxygen Fission in Carboxylic Esters. Part III.*

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Optically active esters of 1-naphthylmethylcarbinol react with carboxylic acids with racemisation, do not react with anhydrous alcohols, but react with alcohols in the presence of water. Optically active esters of phenylmethylcarbinol react similarly with anhydrous formic acid, react with acetic acid only in the presence of water, and do not react with methyl and ethyl alcohols even in the presence of water. Thus, these derivatives react by alkyl–oxygen fission less readily than do the esters of substituted allyl alcohols (Part I, *J.*, 1942, 556) or of *p*-methoxybenzhydrol (Part II, *J.*, 1942, 605). In accordance with this, the tendency to racemisation during the hydrolysis of the hydrogen phthalates with weak alkali is less marked in the examples now discussed than in those given in Parts I and II.

The significance of these observations is briefly discussed and attention is drawn to some other recorded examples of alkyl–oxygen fission in reactions of esters and alcohols.

Certain reactions described in Parts I and II, in particular the formation of neutral phthalic esters and of *p*-tolyl sulphones from hydrogen phthalic esters, have been applied to derivatives of certain substituted benzhydrols and related carbinols. Sulphones have also been prepared from certain of the benzhydrols and from anisyl alcohol by interaction with sodium *p*-toluenesulphinate.

THE (+)hydrogen phthalate, (−)benzoate, and (−)acetate of 1-naphthylmethylcarbinol react with anhydrous formic acid to give *dl*-formate; the (+)hydrogen phthalate and (−)benzoate give *dl*-acetate on reaction with glacial acetic acid. The hydrogen phthalate does not react with anhydrous methyl or ethyl alcohol, but, when the alcohol contains some 30% of water, yields a racemic methyl ether, and an ethyl ether of very low rotatory power.

The (+)hydrogen phthalate, acetate, and monochloroacetate of phenylmethylcarbinol react with anhydrous formic acid, yielding *dl*-formate. The hydrogen phthalate, benzoate, and formate of phenylmethylcarbinol do not react with glacial acetic acid, but, in acetic acid containing some 30% of water, the hydrogen phthalate yields an acetate of low rotatory power, the benzoate yields a racemic acetate, and the solution of the formate undergoes some racemisation. The (+)hydrogen phthalate reacts with monochloroacetic acid (in chloroform solution) with extensive racemisation, but does not react with methyl or ethyl alcohol, either anhydrous or with the addition of some 30% of water.

In a number of the experiments in which reaction occurred, part of the reacting ester was removed before the reaction was complete (see experimental section) and was found to have undergone some racemisation analogous to that which occurs in the reactions of esters of substituted allyl alcohols (Part I, *loc. cit.*).

In the experiments so far reported, the tendency to alkyl–oxygen fission is most marked in the esters of *p*-methoxybenzhydrol (Part II, *loc. cit.*), followed by the substituted allyl esters (Part I, *loc. cit.*). In both these cases the esters react with anhydrous carboxylic acids and alcohols with racemisation. Esters of 1-naphthylmethylcarbinol are somewhat less reactive in this sense: they react with carboxylic acids, but not with anhydrous methyl or ethyl alcohol, though they react with the alcohols when water is added to the medium (*i.e.*, when its ionising power is increased).

Still less reactive are the esters of phenylmethylcarbinol, which react with formic acid but not with acetic acid, and do not react with methyl or ethyl alcohol even in presence of water. This order of reactivity is parallel to the electron-releasing powers of the substituents in the alkyl groups, and is followed by the tendency to alkyl–oxygen fission during alkaline hydrolysis of the hydrogen phthalates. If, in the hydrolysis of the esters described in Parts I and II, weakly alkaline solutions are used, complete racemisation occurs. When the hydrogen phthalate of 1-naphthylmethylcarbinol is hydrolysed by weak alkali (sodium carbonate), some 50% of the product is racemic; hydrolysis of phenylmethylcarbinyl hydrogen phthalate with sodium carbonate gives an alcohol with rotatory power only a little lower than that obtained by hydrolysis with 10N-sodium hydroxide solution.

A number of reactions of types described in Parts I and II and above have been applied to derivatives of various of the following alcohols: Anisylethylcarbinol (I), *o*-chlorobenzhydrol (II), *p*-dimethylaminobenzhydrol (III), p-*methoxy*-p′-*methylbenzhydrol* (IV), *p*-methoxy-*p*′-*iso*propylbenzhydrol (V), o-*methoxyphenyl*-1-*naphthylcarbinol* (VI), phenyl-3:4-methylenedioxyphenylcarbinol (VII), 3:4-*methylenedioxyphenylmethylcarbinol* (VIII), *m*-methoxybenzhydrol (IX). (I), (II), (IV), and (VII) have been obtained in optically active forms, and the optically active hydrogen phthalates of (I) and (II) undergo slight racemisation on hydrolysis with 5N-sodium hydroxide: on hydrolysis with sodium carbonate of the hydrogen phthalate of (I), some 80% racemisation occurs, and of the hydrogen phthalate of (II), 50% racemisation. The corresponding di-ethers are formed, on heating, from (I), (IV), (V), and (VI), but not from (II) or (III). The hydrogen phthalate of (II) does not react with methyl or ethyl alcohol even when the alcohol contains 30% of water; the hydrogen phthalate of (III) reacts with methyl alcohol to give the methyl ether of (III). The hydrogen phthalates of (I), (IV), (V), and (VI), dissolved in a slight excess of aqueous sodium hydroxide, yield the neutral phthalate; the hydrogen phthalate of (II), and the hydrogen succinates of (II), (IV), and (VI), under the same conditions, undergo hydrolysis; the hydrogen succinate of (I) yields an oil which probably contains neutral succinate, but it could not be purified. By interaction of the hydrogen phthalates, dissolved in an equivalent amount of aqueous sodium hydroxide, with sodium *p*-toluenesulphinate, *p*-tolyl sulphones of (I), (II), (IV), (V), (VI), and (VIII) are obtained in approximately quantitative yield; anisyl *p*-tolyl sulphone is formed from anisyl hydrogen phthalate in 30% yield; the hydrogen phthalate (and hydrogen succinate) of (II) and the hydrogen phthalate of (IX) undergo partial hydrolysis. The hydrogen phthalates of (II) and of anisyl alcohol react with sodium *p*-toluenesulphinate in formic acid solution to give the *p*-tolyl sulphones in good yield. The *p*-tolyl sulphones of (I) and (VI) are also formed under similar conditions from their hydrogen succinates. *p*-Tolyl sulphones are also formed, by interaction with sodium *p*-toluenesulphinate, from the acetate of (I) (70% yield) and anisyl acetate (10% yield) in aqueous ethyl alcohol; the acetate of (II) does not react in this solvent, but gives a quantitative yield of sulphone on reaction in formic acid solution, as does also anisyl acetate.

Certain sulphones have also been obtained by interaction of the alcohols with sodium *p*-toluenesulphinate, the solutions becoming alkaline from the concomitant production of sodium hydroxide. In aqueous methyl or ethyl alcohol, sulphones have thus been obtained from *p*-methoxybenzhydrol (20% yield), (III) (100%), and anisyl alcohol (10%); in formic acid solution, anisyl alcohol gives a quantitative yield of the sulphone.

(II), dissolved in a slight excess of dilute hydrochloric acid, reacts with *p*-toluenesulphinic acid to give a quantitative yield of sulphone. This method was used by Hinsberg (*Ber.*, **1917**, **50**, 468) to give the phenyl

sulphone of *pp'*-tetramethyldiaminobenzhydrol (Michler's hydrol); in both reactions the primary function of the hydrochloric acid is presumably as solvent for the aminobenzhydrol, but it will also promote ionic fission of the hydrol by removing the liberated hydroxyl ion as water. The two *p*-dimethylamino substituents in Michler's hydrol result in very easy separation of the hydroxyl group, and the hydrol is known to react with a large number of compounds containing keto-methylenic systems, or other groups from which the resulting carbonium kation can displace a proton (Noelting, *Ber.*, 1891, **24**, 3133; 1902, **35**, 318; Weil, *ibid.*, 1894, **27**, 1403; Möhlau and Heinge, *ibid.*, 1902, **35**, 361; O. Fischer and Weiss, *Z. Farben u. Text. Chem.*, 1902, **1**, 1; Fosse, *Ann. Chim. Phys.*, 1909, **18**, 400; Bogert and Rudermann, *J. Amer. Chem. Soc.*, 1922, **44**, 2612; Humphries, *J.*, 1926, 374).

It is convenient here to draw attention to some other cases of alkyl–oxygen fission. The (−)hydrogen phthalate of 2-naphthylmethylcarbinol reacts with formic acid with racemisation (Collyer and Kenyon, *J.*, 1940, 676). The (−)hydrogen phthalate of 1-furylmethylcarbinol reacts with acetic acid with racemisation and yields a racemic alcohol when hydrolysed with sodium carbonate, whereas optical purity is retained on hydrolysis with 10N-sodium hydroxide (Duveen and Kenyon, *J.*, 1936, 621).

Norris and Rigby (*J. Amer. Chem. Soc.*, 1932, **54**, 2088) have shown that the interaction of *tert.*-butyl alcohol and acetyl chloride yields *tert.*-butyl acetate in the presence of dimethylaniline, and the chloride in the absence of base (see the discussion of analogous reactions of *p*-methoxybenzhydrol with acetyl chloride in Part II).

Cohen and Schneider (*J. Amer. Chem. Soc.*, 1941, **63**, 3382) describe the formation of methyl *tert.*-butyl ether by the reaction of *tert.*-butyl benzoate or 2 : 4 : 6-trimethylbenzoate with methyl alcohol. Burwell (*J. Amer. Chem. Soc.*, 1942, **64**, 1025) describes the acid-catalysed racemisation of (+)-2-butanol; this may be analogous to the acid catalysed racemisation of esters of this alcohol and of (+)-2-octanol which we have under investigation (*Nature*, 1941, **148**, 196). With regard to the footnote to Part II (*loc. cit.*) it should be observed that the reaction of 3 : 3 : 3-trichloro-1-nitro-2-acetoxypropane with ammonia may involve intermediate formation of a nitro-olefin (Irving, *J.*, 1936, 797); both this mechanism and the bimolecular replacement mechanism would involve alkyl–oxygen fission.

Experimental.

dl-1-Naphthylmethylcarbinol (Grignard's method, yield 62%, m. p. 67°) was converted into its hydrogen phthalate (m. p. 132°) and this into the brucine salt (m. p. 155°) by the usual method. The less soluble fraction of the salt, recrystallised four times from acetone and decomposed (acetone + hydrochloric acid), yielded the (+)hydrogen phthalate (see Table), and this on hydrolysis and steam distillation gave the (−)carbinol (see Table), m. p. 48°. A crystalline alkaloidal salt of the (−)hydrogen phthalate could not be prepared; the hydrogen phthalate from the mother liquor from the above recrystallisations was purified *via* the ammonium salt and dissolved in carbon disulphide. Repeated inoculation with *dl*-hydrogen phthalate, followed by filtration, removed the *dl*-ester; the (−)ester was obtained as a gum from the residual solution, and converted into the (+)carbinol, m. p. 46° after recrystallisation from ether–light petroleum. The rotatory powers given in the Table are slightly higher than those recorded by Pickard and Kenyon (*J.*, 1914, **105**, 1130).

Rotatory Powers of (+) *and* (−)1-*Naphthylmethylcarbinol and the* (+)*Hydrogen Phthalate in Ethyl Alcohol* (*l*, 2) *at* 20°.

	c.	$[\alpha]_{5893}$	$[\alpha]_{5780}$	$[\alpha]_{5461}$	$[\alpha]_{4358}$
(+)Carbinol	4·81	+76·4°	+80·7°	+91·9°	+167°
(−)Carbinol	4·94	−78·9	−80·8	−97·8	−150
(+)Hydrogen phthalate	5·10	+73·0	—	+81·7	—

Esters of 1-*Naphthylmethylcarbinol.*—*Acetates* (from the carbinol, using pyridine and acetic anhydride). The dl-*acetate* had b. p. 132°/2 mm., 160°/10 mm.; $n_D^{20°}$ 1·5805 (Found: C, 78·4; H, 7·0. $C_{14}H_{14}O_2$ requires C, 78·5; H, 6·6%). The (−)acetate, from the (−)carbinol, had b. p. 173°/15 mm.; $\alpha_{6438}^{22°}$ −8·20°; $\alpha_{5893}^{22°}$ −11·17°; $\alpha_{5780}^{22°}$ −11·71°; $\alpha_{5461}^{22°}$ −13·27°; $\alpha_{4358}^{22°}$ −23·0 (*l*, 0·25).

Benzoates (benzoyl chloride–pyridine). The dl-*ester*, recrystallised from ether–light petroleum, had m. p. 69—70° (Found: C, 82·6; H, 5·8. $C_{18}H_{14}O_2$ requires C, 82·7; H, 5·8%). The (−)ester [from the (+)carbinol] did not crystallise; b. p. 192°/3·5 mm.; $[\alpha]_{5893}^{20°}$ −72·4°; $[\alpha]_{5461}^{20°}$ −88·9°; $[\alpha]_{4358}^{20°}$ −176·0° (*l*, 2; *c*, 5·0 in ethyl alcohol); $\alpha_{5893}^{10°}$ −26·86° (homog., *l*, 0·25).

Esters of Phenylmethylcarbinol.—(+) and (−)Phenylmethylcarbinols were prepared as described by Downer and Kenyon (*J.*, 1939, 1156); the formate is described by Arcus, Balfe, and Kenyon (*J.*, 1938, 485). The (+)acetate had b. p. 106°/10 mm.; $n_D^{18°}$ 1·4983 (Kenyon, Phillips, and Taylor, *J.*, 1933, 173, give b. p. 109°/18 mm.; $n_D^{20°}$ 1·5045); $\alpha_{5893}^{19°}$ +30·75°; $\alpha_{5780}^{19°}$ + 32·40°; $\alpha_{5461}^{19°}$ +37·48°; $\alpha_{4358}^{19°}$ +67·8° (*l*, 0·25).

The dl-*benzoate* had b. p. 123·6°/2 mm., $n_D^{21°}$ 1·5588 (Found: C, 80·2; H, 6·2. $C_{18}H_{14}O_2$ requires C, 79·8; H, 6·2%). The (+)benzoate [from the (+)carbinol] had b. p. 137—141°/6 mm.; $n_D^{21°}$ 1·5593; $\alpha_{5893}^{24°}$ −4·40°; $\alpha_{5780}^{22°}$ −4·89°; $\alpha_{5461}^{22°}$ −5·89°; $\alpha_{4358}^{22°}$ −13·34° (*l*, 0·25).

The dl-*monochloroacetate* (acid chloride and pyridine in light petroleum) had b. p. 135—140°/16 mm.; $n_D^{21°}$ 1·5177 (Found: Cl, 17·3. $C_{10}H_{11}O_2Cl$ requires Cl, 17·9%). The (+)chloroacetate [from (+)carbinol] had b. p. 135—138°/16 mm.; $n_D^{21°}$ 1·5141; $\alpha_{6438}^{21°}$ +27·21°; $\alpha_{5893}^{21°}$ 32·37°; $\alpha_{5780}^{21°}$ +34·07°; $\alpha_{5461}^{21°}$ +37·08°; $\alpha_{4358}^{21°}$ +70·81° (*l*, 0·25).

Reactions of 1-*Naphthylmethylcarbinyl Esters.*—*Hydrogen phthalate.* (i) With glacial acetic acid. (*a*) A solution of the (+)ester (2·82 g.) in 25 c.c. of acid, warmed on the steam-bath, had the following rotatory powers: α_{5893} (*l*, 2) initial, +6·86°; after 10 hours, +4·24°; 23 hours, + 1·62°; 32 hours, zero. The mixture then yielded phthalic acid (0·5 g.) and *dl*-acetate (1·3 g.), b. p. 174—175°/15 mm. (Found: C, 78·7; H, 6·4%).

(*b*) A solution of the (+)ester (4·86 g.) in 50 c.c. of acid had α_{5893} (*l*, 2), initial +5·78°; after 9 hours on steam-bath, +2·69°. The mixture then yielded a hydrogen phthalate with $[\alpha]_{5893}$ +52·2°; $[\alpha]_{5461}$ +64·5° in ethyl alcohol (*l*, 2).

(ii) With aqueous acetic acid. (*a*) A solution of the (+)phthalate (6·2 g.) in acetic acid (60 c.c.) and water (15 c.c.) after being warmed for 1 hour yielded *dl*-acetate, b. p. 174°/15 mm.; $n_D^{20°}$ 1·580 (1·00 g. required for hydrolysis 0·047 g. of KOH. Calc. for $C_{14}H_{14}O_2$: 0·0465 g. of KOH).

(*b*) A solution of (+)phthalate (5 g.) in acetic acid (50 c.c.) and water (13 c.c.) had $\alpha_{5893}^{20°}$ +8·0° (*l*, 2). After 1½ hours on the steam-bath it had α_{5893}^{20} +2·1° (*l*, 2) and then yielded a hydrogen phthalate with $[\alpha]_{5893}$ +54·3° in ethyl alcohol (*c*, 6·4).

(iii) With formic acid. From the (+)phthalate (2·5 g.), in formic acid (20 c.c.), after 1 hour at 45°, *dl*-formate (1 g.) was obtained, b. p. 166°/18 mm.; $n_D^{18°}$ 1·5940 (Found: C, 77·3; H, 6·1. $C_{13}H_{12}O_2$ requires C, 77·8; H, 6·0%). At 37° no reaction occurred, and at 100° there was much decomposition.

(iv) With methyl alcohol. No reaction occurred with anhydrous methyl alcohol. The *dl*-phthalate, after being heated under reflux for 3 days with methyl alcohol (50 c.c.) and water (15 c.c.), gave dl-1-(1′-*naphthyl*)*ethyl methyl ether*, b. p. 140—143°/9 mm.; $n_D^{17°}$ 1·5928 (Found: C, 83·9; H, 7·4. $C_{13}H_{14}O$ requires C, 83·9; H, 7·5%). The (+)phthalate (1 g.) in methyl alcohol (20 c.c.) and water (4 c.c.) gave the following values of $\alpha_{5893}^{20°}$ (*l*, 2): initial, + 5·9°; refluxed for 40 hours, +1·5°; refluxed for 64 hours, +0·1°; after 64 hours the solution yielded the *dl*-ether, b. p. 132°/7 mm.; $n_D^{18°}$ 1·5862.

(v) With ethyl alcohol. No reaction occurred with the anhydrous alcohol. The *dl*-phthalate (5 g.) refluxed for 3 days in ethyl alcohol (50 c.c.) and water (16 c.c.) gave dl-1-(1′-*naphthyl*)*ethyl ethyl ether*, b. p. 144°/7 mm.; $n_D^{18°}$ 1·5870 (Found: C, 84·2; H, 8·0. $C_{14}H_{16}O$ requires C, 84·0; H, 8·0%). A solution of the (+)phthalate (3·9 g.) in ethyl alcohol (40 c.c.) and water (10 c.c.) gave the following values of $\alpha_{5893}^{20°}$ (*l*, 2) (duration of refluxing in brackets): (0 hour) +10·6°; (60 hours) +1·3°; (72 hours) +1·2°. After 72 hours the solution yielded an ethyl ether (1·9 g.), b. p. 149°/7 mm., $n_D^{20°}$ 1·5839, $[\alpha]_{5893}$ +2·20° in ethyl alcohol (*l*, 2·36; *c*, 5·00), and a hydrogen phthalate (1·4 g.), $[\alpha]_{5893}$ +8·9° in ethyl alcohol.

(vi) Hydrolysis of the hydrogen phthalate. The phthalate (8 g., 1 mol., $[\alpha]_{5893}$ +18·66° in ethyl alcohol, *l*, 2; *c*, 2·04), dissolved in a little ethyl alcohol, was heated with 6 c.c. of 10N-sodium hydroxide (2·5 mols.) first on the steam-bath, then in a current of steam. From an ethereal extract of the residual liquid, 3·1 g. of crude alcohol were obtained, m. p. 50—57°; $[\alpha]_{5893}$ −21·35° in ethyl alcohol (*l*, 2; *c*, 2·58). This alcohol was converted into its hydrogen phthalate which was purified by precipitation from ammoniacal solution; yield 3·5 g., $[\alpha]_{5893}$ +18·3° (*l*, 2; *c*, 2·68) in ethyl alcohol.

In a similar experiment with 8 g. of the same phthalate, using 6·7 g. (2·5 mols.) of sodium carbonate instead of sodium hydroxide for the hydrolysis, 1·2 g. of crude alcohol were obtained. The hydrogen phthalate, purified by precipitation from solution in sodium carbonate, had $[\alpha]_{5893}$ +7·53° (*l*, 2; *c*, 2·1) in ethyl alcohol.

Benzoate. (i) With glacial acetic acid. The (−)benzoate (5 g.) did not react at room temperature with acetic acid (50 c.c.); at 80°, the solution racemised in 3 days and then yielded *dl*-acetate, b. p. 173°/15 mm.; $n_D^{20°}$ 1·580. The initial solution had α_{5893} −14·8° (*l*, 2); when this had fallen to −6·7° (37 hours) the benzoate was recovered from a portion; it had m. p. 117°, $[\alpha]_{5893}$ −28·9° in ethyl alcohol (*l*, 2; *c*, 3·6).

(ii) With formic acid. From a solution of (−)benzoate (1 g.) in formic acid (20 c.c.) after 4 hours at room temperature, *dl*-formate (0·6 g.) was obtained, b. p. 168°/18 mm.; $n_D^{21°}$ 1·5911.

Acetate. With formic acid. (i) (−)Acetate (0·505 g.), made up to 10 c.c. with formic acid, gave the following mutarotation data of $\alpha_{5893}^{15°}$ (*l*, 1): initial, −1·21°; 3 mins. after solution, −0·86°; 4·5 mins., −0·67°; 6·0 mins., −0·65°, 7·6 mins., −0·52°; 8·9 mins., 0·46°; 10·2 mins., −0·40°; 11·8 mins., −0·34°; 13·25 mins., −0·28°; 16·25 mins., −0·20°; 19·25 mins., −0·11°.

(ii) (−)Acetate (0·542 g.), made up to 10 c.c. with formic acid, gave the following $\alpha_{5893}^{21°}$ (*l*, 1): initial, −1·1°; 0·15 min., −1·0°; 7·5 mins., −0·03°. The two solutions, when mixed, yielded *dl*-formate, b. p. 161°/10 mm.; $n_D^{19°}$ 1·5932 (1·000 g. required for saponification 47·9 mg. of KOH).

Reactions of Phenylmethylcarbinyl Esters.—Hydrogen phthalate. (i) With acetic acid. No reaction occurred with glacial acetic acid at 100°. 5·2 G. of (+)phthalate in 40 c.c. of acetic acid and 15 c.c. of water, kept at 100°, had $\alpha_{5893}^{20°}$ (*l*, 2): initial, +1·54°; 40 mins., +0·98°; 90 mins., +0·53°. The solution then yielded *dextro*-acetate * (1·2 g.), b. p. 104°/11 mm., $\alpha_{5893}^{18°}$ +0·97° (*l*, 0·25), and *lævo*-phthalate, 1·7 g., $[\alpha]_{5893}$ −27·5° in ethyl alcohol.

(ii) With formic acid. (+)Phthalate (1 g.) in formic acid (10 c.c.) after 1 hour at 37° yielded *dl*-formate, b. p. 89—90°/15 mm.; $n_D^{20°}$ 1·5055.

(iii) With chloroacetic acid. 4 G. in chloroform (10 c.c.) after 7 hours on the steam-bath yielded *dextro*-chloroacetate (5 g.), b. p. 138°/17 mm.; $n_D^{21°}$ 1·5129; $\alpha_{5461}^{20°}$ +0·28° (*l*, 0·25).

(iv) Hydrolysis of the hydrogen phthalate. The phthalate (7 g., $[\alpha]_{5893}$ −12·73°, *l*, 2; *c*, 2·28 in ethyl alcohol), dissolved in a little ethyl alcohol, was heated with 6 c.c. of 10N-sodium hydroxide (2·5 mols.) first on the steam-bath, then in a current of steam. From the distillate, by extraction with ether, the alcohol was obtained, $\alpha_{5893}^{18°}$ +4·28° (*l*, 0·25). The hydrogen phthalate from this alcohol was purified by precipitation from ammonia solution. Yield 4·0 g., $[\alpha]_{5893}$ −11·73° in ethyl alcohol (*l*, 2; *c*, 2·5).

In a similar experiment, 7 g. of the same phthalate were hydrolysed with 12 g. (2·5 mols.) of sodium carbonate. The purified phthalate (3 g.), into which the liberated alcohol was reconverted, had $[\alpha]_{5893}$ −10·51° (*l*, 2; *c*, 3·1) in ethyl alcohol.

(v) Methyl and ethyl alcohols, dry or in presence of water, did not react with the phthalate when heated under reflux for 72 hours.

Acetate with formic acid. dextro-Acetate (0·5 g.) in formic acid (10 c.c.) gave the following values of $\alpha_{5893}^{27°}$ (*l*, 2): initial, +5·35°; 3·75 mins., +4·35°; 9 mins., +3·68°; 13·5 mins., +3·12°; 20·5 mins., +2·36°; 28 mins., +1·85°; 32·2 mins., +1·46°; 43·2 mins., +1·11°; 55 mins., +0·69°; 70·5 mins., +0·24°. A solution of the same concentration gave $\alpha_{5893}^{19°}$ (*l*, 2): initial, +13·15°; 15 mins., +9·2°; 24 mins., +9·0°; 35 mins., +8·0°; 53 mins., +6·6°; 66 mins., +5·7°; 80 mins., +4·9°; 98 mins., +4·12°; 116 mins., +3·55°; 140 mins., +2·75°; 159 mins., +2·08°; 192 mins., +1·22°; 252 mins., +0·15°. The two solutions were finally mixed and yielded *dl*-formate (0·6 g.), b. p. 91°/15 mm.; $n_D^{20°}$ 1·506.

Benzoate with acetic acid. No reaction occurred with dry acetic acid. (−)Benzoate (1 g.) in acetic acid (20 c.c.) and water (4 c.c.), after 15 hours on the steam-bath, yielded *dl*-acetate, b. p. 98°/10 mm.; $n_D^{20°}$ 1·5047.

Monochloroacetate with formic acid. A solution of the (+)chloroacetate (1 g.) in anhydrous formic acid (20 c.c.) became optically inactive after 7 days at room temperature, and then yielded the *dl*-formate (0·6 g.), b. p. 90°/15 mm.; $n_D^{20°}$ 1·5045.

Formate. (i) With acetic acid. No reaction occurred with glacial acetic acid. The rotatory power of a solution of (−)formate (0·6 g.) in acetic acid (12 c.c.) and water (2 c.c.) fell from $\alpha_{5893}^{20°}$ −2·08° (*l*, 1) to −1·02° after 4 weeks at room temperature.

(ii) With formic acid. A solution of the (−)formate (0·9 g.) in formic acid (16 c.c.) became inactive after 25 hours at room temperature and then yielded the *dl*-formate, b. p. 90°/15 mm.; $n_D^{20°}$ 1·505.

Preparation of Carbinols (I)—(IX).—All Grignard complexes were decomposed with ice and ammonium chloride.

Anisylethylcarbinol (I). Grignard reaction with anisaldehyde (Hell and Hoffmann, *Ber.*, 1904, **37**, 4190; 1905, **38**, 1678). 80% Yield, b. p. 143°/17 mm.

o-Chlorobenzhydrol (II). Grignard reaction with *o*-chlorobenzaldehyde (Tschitchibabin and Schlesler, *J. Russ. Phys. Chem. Soc.*, 1925, **56**, 149). 70% Yield, m. p. 65—66°.

* In this and the following papers the prefixes *dextro* and *lævo* denote optically impure substances.

p-*Dimethylaminobenzhydrol* (III). From the ketone (Hurd and Webb, *Org. Synth.*, Coll. Vol. I, p. 213) reduced in alcohol by sodium amalgam (Albrecht, *Ber.*, 1888, **21**, 3293) or preferably by zinc powder and sodium hydroxide (1 g. each per g. of ketone) in alcohol (20 c.c. per g. of carbinol). 90% Yield, m. p. 69—70°.

p-*Methoxy*-p′-*methylbenzhydrol* (IV). Grignard reaction with anisaldehyde. 80% Yield of the *compound*, m. p. 61—62° from ethyl ether–light petroleum (Found: C, 78·8, H, 7·0. $C_{15}H_{16}O_2$ requires C, 78·9; H, 7·0%).

p-*Methoxy*-p′-*isopropylbenzhydrol* (V). Grignard reagent (from *p*-bromocumene, Jacobsen, *Ber.*, 1879, **12**, 430) reacted with anisaldehyde. 55% Yield, m. p. 63—64° from ether–light petroleum.

o-*Methoxyphenyl*-1-*naphthylcarbinol* (VI). Grignard reaction with *o*-methoxybenzaldehyde. After preparation of the naphthylmagnesium bromide, it is desirable to add 500 c.c. of benzene per g.-mol. to prevent the reagent separating as a hard, slowly reactive mass. 60% Yield of the *compound*, m. p. 102—103° from ether–light petroleum (Found: C, 82·1; H, 5·9. $C_{18}H_{16}O_2$ requires C, 81·8; H, 6·1%).

Phenyl-3:4-*methylenedioxyphenylcarbinol* (VII). Grignard reagent with piperonal. Yield 70%, b. p. 235—236°/23 mm.

3:4-*Methylenedioxyphenylmethylcarbinol* (VIII). Grignard reagent with piperonal. 80% Yield of the *compound*, b. p. 146—148°/17 mm., $n_D^{15°}$ 1·5594 (Found: C, 65·1; H, 5·9. $C_9H_{10}O_3$ requires C, 65·1; H, 6·0%).

m-*Methoxybenzhydrol* (IX). Grignard reagent with *m*-methoxybenzaldehyde. B. p. 195—197°/8 mm.

Hydrogen phthalates. From the carbinol (1 mol.), phthalic anhydride (1 mol.), and pyridine (1·1 mols.). For (I), (II), (VII), (VIII), (IX), and anisyl alcohol, the reagents were kept at 60° for 1—5 hours; and hydrogen phthalate then precipitated, by addition of acetone and slight excess of hydrochloric acid, as an oil which slowly solidified in ice-water. For (IV), (V), and (VI), benzene (1 c.c. per g. of carbinol) was added to the reagents, and reaction conducted at 20° for 3 days. On dilution with acetone and extraction of the pyridine with dilute hydrochloric acid, the hydrogen phthalate crystallised from the benzene (this method is advantageous). *M* determined by rapid titration (cold) with 0·1*N*-sodium hydroxide.

Hydrogen Phthalates.

Carbinol.	Crystallised from:	M. p.	Formula.	*M* (found).	*M* (calc.).
(I)	Ether–ligroin	72—74°	$C_{18}H_{18}O_5$	319	314
(II)	Ligroin	177—178	$C_{21}H_{15}O_4Cl$	362	366
(IV)	Benzene–ligroin	128	$C_{23}H_{20}O_5$	377	376
(V)	,,	110	$C_{25}H_{24}O_5$	398	404
(VI)	Benzene	174—175	$C_{26}H_{20}O_6$	413	412
(VII)	Ether–ligroin	121	$C_{23}H_{18}O_6$	378	376
(VIII)	,,	94	$C_{17}H_{14}O_6$	314	314
(IX)	,,	120—122	$C_{22}H_{18}O_5$	365	362
Anisyl alcohol	Methylene chloride–ligroin	68			

Hydrogen Succinates. These were prepared in the same way as the corresponding hydrogen phthalates.

(I)	Ether–ligroin	36—37°	$C_{14}H_{18}O_5$	266	267
(II)	Ligroin	109—110	$C_{17}H_{15}O_4Cl$	318	318
(IV)	Ether–ligroin	59—60	$C_{19}H_{20}O_5$	306	308
(VI)	Benzene–ligroin	126	$C_{22}H_{20}O_5$	366	364

Optically Active Hydrogen Phthalates and Succinates.—Prepared by the usual method (see, *e.g.*, Part II), the solvent being acetone, except for (II), for which equal parts of acetone and methyl alcohol were used.

Phthalates of (I) from cinchonidine salt. The less soluble, twice recrystallised, had m. p. 162—163° and gave a *dextro*-hydrogen phthalate, m. p. 76—78°; $[\alpha]_{5893}^{18°}$ +7·8° in benzene (*l*, 2; *c*, 4·8). From the first mother liquor, a *lævo*-phthalate was obtained, m. p. 73—76°; $[\alpha]_{5893}^{20°}$ −10·5° in benzene (*l*, 2; *c*, 6·5).

Hydrogen succinates, similarly showed $[\alpha]_{5893}^{20°}$ −32·5° and +22·5° respectively in ethyl alcohol (*l*, 2; *c*, 2·0).

Hydrogen phthalates of (II) from brucine salt. The less soluble, 4 times recrystallised, had m. p. 217° and gave a phthalate with $[\alpha]_{5893}^{20°}$ +11·2° in ethyl alcohol. When this phthalate was recrystallised from carbon disulphide, the more *dextro*-salt remained in solution and had m. p. 66—68°; $[\alpha]_{\lambda}^{20°}$ in ethyl alcohol (*l*, 2; *c*, 1·0); λ_{6438} +13·0°; λ_{5893} +14·4°; λ_{5461} +16·6°; λ_{4358} +25·9°; and $[\alpha]_{\lambda}^{20°}$ in benzene (*l*, 2; *c*, 1·6); λ_{5893} +13·5°; λ_{5780} +15·2°; λ_{5461} +15·4°; λ_{4358} +20·9°. The mother liquor from the first brucine salt gave a hydrogen phthalate, which was dissolved in methylene chloride; the less *lævo*-salt crystallised out, and the more soluble fraction was hydrogen phthalate, m. p. 69—71°, with $[\alpha]_{5893}^{20°}$ −15·6° in ethyl alcohol (*l*, 2; *c*, 2·6).

The phthalate of (IV) from the quinidine salt, several times recrystallised, had $[\alpha]_{5893}^{20°}$ (*l*, 2; *c*, 1·5): in acetone, −11·7°; in ethyl alcohol, −9·7°; in nitromethane, −3·6°; in chloroform, −11·0°. In all these solvents racemisation occurred, the approximate half-life periods (hours) being: in acetone, 25; in ethyl alcohol, 18; in chloroform, 3; in nitromethane, $1\frac{1}{2}$.

The quinidine salt of (VII), three times recrystallised, gave phthalate, m. p. 114°. The first mother liquor gave a *dextro*-phthalate, m. p. 115—116° (after recrystallisation from ether–ligroin), $[\alpha]_{5893}^{20°}$ +20·0° (*l*, 2; *c*, 1·5) in benzene.

Optically active forms of (II). From the hydrogen phthalates (5 g.) in ethyl alcohol (25 c.c.) with sodium hydroxide (1·5 g.; 2·5 mols.) heated under reflux for 1 hour. On dilution with water, the carbinol was precipitated (2·4 g.) and was then recrystallised from ligroin.

The *dextro*-hydrogen phthalate gives *lævo*-carbinol, m. p. 65° with $[\alpha]_{\lambda}^{18°}$ (*l*, 2) in ethyl alcohol (*c*, 2·1): λ_{5893} −4·5°; λ_{5780} −7·5°; λ_{5461} −7·7°; λ_{4358} −18·0°. In carbon disulphide (*c*, 2·5): λ_{5893} −3·2°; λ_{5780} −6·5°; λ_{5461} −6·6°; λ_{4358} −17·1°. In benzene (*c*, 3·2): λ_{5893} −6·6°; λ_{5780} −8·0°; λ_{5461} −8·0°; λ_{4358} −14·5°: In ether (*c*, 1·9): λ_{5893} −7·1°; λ_{5780} −11·7°; λ_{5461} −11·7°. λ_{4358} −30·4°. The *dextro*-carbinol had $[\alpha]_{5893}^{22°}$ +4·7° (*l*, 2; *c*, 2·3) in ethyl alcohol.

Experiments on hydrolysis of lævo-*phthalates of* (I) *and* (II). (i) Hydrolysis of *lævo*-phthalate of (I) (all $[\alpha]_{5893}^{20°}$ in benzene, *l*, 2), using in each experiment 6·3 g. of hydrogen phthalate of [α] −10·5°, with 2·5 mols. of alkali, 20 minutes at 70°, followed by dilution with water and conversion of the precipitated carbinol into hydrogen phthalate, which (to avoid separation of stereoisomerides) was taken without recrystallisation for [α] observation.

(*a*) With sodium hydroxide (from 1·1 g. of sodium) in 96% ethyl alcohol (30 c.c.). The re-formed phthalate had [α] −9·7° (*c*, 2·3).

(*b*) With 10 c.c. of 5N-sodium hydroxide. The re-formed phthalate had [α] −7·7°.

(*c*) With 5 g. of sodium carbonate in 30 c.c. of water. The re-formed phthalate had [α] −2·3° (*c*, 2·2).

(ii) Hydrolysis of *lævo*-phthalate of (II) (all $[\alpha]_{5893}^{20°}$ in ethyl alcohol, *l*, 2). In each experiment, 7 g. of hydrogen phthalate ([α] −6·34°), with 2·5 mols. of alkali, 30 minutes at 70°, procedure as above.

(*a*) With sodium hydroxide (from 1·1 g. of sodium) in 96% ethyl alcohol (20 c.c.). The carbinol obtained had [α] +1·9° (*c*, 1·9), and its phthalate had [α] −6·1° (*c*, 1·8).

(*b*) With 11 c.c. of 5N-sodium hydroxide, gave carbinol, [α] +1·7° (*c*, 1·8), and phthalate, [α] −5·4° (*c*, 2·4).

(*c*) With 6 g. of sodium carbonate in 50 c.c. of water, gave carbinol, [α] +1·0° (*c*, 1·9) and phthalate, [α] −1·9° (*c*, 2·2).

Chlorides of (II), (III), *and* (VI).—(*M* by hydrolysis with N-sodium hydroxide).

(II) The carbinol (2·8 g.), thionyl chloride (1·5 g.), and pyridine (2·5 g.) after several hours at 20°, gave the chloride (1·5 g.) which, extracted with ligroin, had b. p. 148—149°/9 mm. (Found: *M*, 237. Calc. for $C_{13}H_{10}Cl_2$: *M*, 237). The chloride from carbinol of $[\alpha]_{5893}^{19°}$ −6·6° in benzene, on hydrolysis with 0·3N-sodium hydroxide, gave carbinol of $[\alpha]_{5893}^{20°}$ −5·2° in benzene. The chloride did not react with water.

(III) The carbinol on trituration with concentrated hydrochloric acid (excess removed over lime) gave chloride which separated as an oil from ligroin (Found: *M*, 250. Calc. for $C_{15}H_{13}OCl$: *M*, 247).

(VI) From the carbinol, by the same method as for the chloride of (III). M. p. 142° (from ligroin) (Found: *M*, 281. Calc. for $C_{18}H_{15}OCl$: *M*, 283). The chloride (m. p. and mixed m. p. 142°) was also obtained, and isolated as above, on heating the hydrogen phthalate of (VI) for several hours with concentrated hydrochloric acid.

Di-ethers of (I), (IV), (V), *and* (VI).—That of (I) remained as a residue on distillation thereof, and had b. p. 209°/12 mm., 190°/9 mm., 179°/7 mm. The others were obtained in about 80% yield on heating the carbinols till no more water was evolved [(IV), 10 mins. at 140°; (V), 25 mins. at 140°; (VI), 10 mins. at 195°]. Ethers were not obtained on heating (II) at 165° or (III) at 210°.

Di-ethers of:	Crystallised from:	M. p.	Formula.	Found (%). C.	Found (%). H.	Required (%). C.	Required (%). H.
(I)	Liquid (see b. p. above)	—	$C_{20}H_{26}O_3$	76·7	8·3	76·4	8·3
(IV)	Ether–methyl alcohol	103—104°	$C_{30}H_{30}O_3$	82·4	6·8	82·1	6·9
(V)	,, ,,	101—102	$C_{24}H_{30}O_3$	82·9	7·7	82·6	7·7
(VI)	Benzene or methylene chloride–ligroin	261—262	$C_{36}H_{30}O_5$	84·9	5·6	84·7	5·9

The methyl ether of (III) separated on cooling a methyl-alcoholic solution of (III) which had been heated under reflux for a few minutes, and was recrystallised from methyl alcohol; m. p. 47—48° (Found: N, 5·5. $C_{16}H_{19}ON$ requires N, 5·5%). Anisyl acetate, from the alcohol and acetic anhydride, has b. p. 139—140°/16 mm., 258—261°/758 mm., $n_D^{15°}$ 1·515 (Tiffeneau, *Bull. Soc. chim.*, 1911, **9**, 827; Vavon, *Ann. Chim.*, 1914, **1**, 158).

Neutral Phthalic Esters.—Prepared as in Part II, the hydrogen phthalate being dissolved in a slight excess of aqueous sodium hydroxide (10—20 c.c. of 0·3N per g. of phthalate). The hydrogen phthalate of (II) did not yield a neutral ester, but underwent some hydrolysis; that of (I) gave an impure neutral ester which would not crystallise and was contaminated with a little carbinol, 0·96 g. yielding, on hydrolysis, 0·38 g. of carbinol (Calc.: 0·34 g.) and 0·28 g. of phthalic acid (Calc.: 0·35 g.). That of (V) gave impure neutral ester as an uncrystallisable oil, 3 g. giving 1·9 g. carbinol on hydrolysis (Calc.: 2·2 g.). The hydrogen phthalates of (IV) and (VI) gave crystalline neutral *esters*, as below:

Neutral phthalate of:	Deposition complete after:	Yield (%).	Crystallised from:	M. p.	Formula.	Found (%). C.	Found (%). H.	Required (%). C.	Required (%). H.
(IV)	30 mins.	80	Ether–ligroin	116—117°	$C_{38}H_{34}O_6$	81·8	5·9	82·1	6·1
(VI)	7 days	40	Benzene–ligroin	222—223	$C_{24}H_{34}O_6$	80·2	5·2	80·2	5·2

The hydrogen succinates of (II), (IV), and (VI) underwent extensive hydrolysis under the above conditions. That of (I) deposited an oil (50% yield) which, from the amount of alkali needed for its hydrolysis and recovery of carbinol therefrom, apparently contained 70% of neutral ester and 30% of carbinol.

p-*Tolyl Sulphones from Hydrogen Phthalates.*—(See Table.) Prepared as in Part II (*loc. cit.*), using equimolecular amounts of phthalate and sodium *p*-toluenesulphinate, in a slight excess of aqueous sodium hydroxide, *e.g.*, 3·8 g. phthalate of (IV), 34 c.c. of 0·3N-sodium hydroxide, added to 2·2 g. of sodium *p*-toluenesulphinate in 50 c.c. of water. In the same way, sulphones were obtained from the hydrogen succinates of (I) (30%) and (VI) (90%). The phthalate and succinate of (II) gave no sulphone, but underwent partial hydrolysis under these conditions. The phthalate (4 g.) of (II) and sodium *p*-toluenesulphinate (3·5 g.) in formic acid (30 c.c.) at 70° for 10 hours, yielded the *sulphone*, precipitated by addition of water (90% yield). Anisyl hydrogen phthalate (1·1 g.) and sodium *p*-toluenesulphinate (0·8 g.) in formic acid at 20° (for 3 hours) yielded the *sulphone* (90%), precipitated by addition of water after removal of phthalic acid precipitate.

p-Tolyl sulphone of:	Pptn. from aq. solution ceased after:	Yield (%).	Crystallised from:	M. p.	Formula.	Found: S, %.	Required: S, %.
(I)	1 day, 20°	100	Aqueous alcohol	124°	$C_{17}H_{20}O_3S$	10·4	10·5
(II)	—	—	Alcohol	114	$C_{20}H_{17}O_4ClS$	9·1	9·0
(III)	—	—	Benzene	186	$C_{22}H_{23}O_3NS$	8·5	8·8
(IV)	30 mins., ,,	95	Alcohol	93—94	$C_{23}H_{22}O_3S$	8·8	8·8
(V)	2 hours ,,	90	,,	123—124	$C_{24}H_{26}O_3S$	8·0	8·1
(VI)	4 days ,,	95	,,	188—189	$C_{25}H_{22}O_5S$	7·7	8·0
(VII)	3 days ,,	50	Acetic acid	146	$C_{21}H_{18}O_4S$	8·8	8·8
(VIII)	1 day ,,	45	Alcohol	150	$C_{16}H_{16}O_4S$	10·2	10·5
Anisyl alcohol	3 hours, 80°	30	,,	120—121	$C_{15}H_{16}O_3S$	11·9	11·6

p-*Tolyl sulphone from* p-*methoxybenzhydryl acetate.* Preparation of the acetate is given in Part II (*loc. cit.*). The sulphone was identified by mixed m. p. with an authentic specimen (Part II). The acetate (2·1 g.) was heated at 80° in 50 c.c. of 50% aqueous ethyl alcohol, with proportions of sodium hydroxide and *p*-toluenesulphinate as given below, until precipitation ceased (time, see below).

Mols. per mol. of acetate: Sodium hydroxide	1·5	0·07	0·07	0·07	0
Sodium *p*-toluenesulphinate	1	4	2	1	2
Time	2 hours	2 hours	40 mins.	10 mins.	1 hour
Yield of sulphone (%)	nil	92	88	84	70
	93% hydrolysis				

Anisyl p-*Tolyl Sulphone from Anisyl Acetate.*—The acetate (0·9 g.), sodium *p*-toluenesulphinate (1·1 g.), and 0·3 c.c. of 0·3N-sodium hydroxide in 30 c.c. of 30% aqueous ethyl alcohol, after 6 hours at 70°, on dilution with water yielded the sulphone (0·2 g.; 14%), m. p. and mixed m. p. 119—120°. The acetate (1·5 g.) and sodium *p*-toluenesulphinate (1·8 g.) in 40 c.c. of formic acid, after 8 hours at 130°, on dilution with water yielded the sulphone (2·1 g.; 90%), m. p. 119—120°.

The *p*-tolyl sulphones of (IV) and (VI) were also prepared by reaction of the respective chlorides with sodium *p*-toluenesulphinate in aqueous acetone.

Preparation of p-*Tolyl Sulphones from Carbinols.*—(i) From *p*-methoxybenzhydrol (2 g.) and sodium *p*-toluenesulphinate (2 g.) in 60 c.c. of 60% aqueous alcohol, during 4 hours at 80°, the hydrol (1·5 g.), m. p. and mixed m. p. 65°, separated. On cooling the now alkaline solution, the sulphone (0·7 g.; 20%) separated, m. p. and mixed m. p. 159°.

(ii) From (III) (0·7 g.) and sodium *p*-toluenesulphinate (0·7 g.), in 30 c.c. of 60% aqueous methyl alcohol, during 5 days at 20°, the sulphone (1 g.) separated, m. p. and mixed m. p. 185—186°.

(iii) From anisyl alcohol (4·5 g.) and sodium *p*-toluenesulphinate (10 g.) in 100 c.c. of 50% aqueous ethyl alcohol, after 5 hours at 80°, the sulphone (0·8 g., 10%) separated on addition of water; recrystallised from ethyl alcohol it had m. p. and mixed m. p. 120—121° (Found: S, 11·9. Calc: S, 11·6%). Also, from anisyl alcohol (2·5 g.) and sodium *p*-toluenesulphinate (3·9 g.) in 100 c.c. of formic acid, after 6 hours at 80°, the sulphone crystallised on addition of water (3·8 g.; quantitative), m. p. and mixed m. p. 120°.

Reaction of (III) *with* p-*toluenesulphinic acid.* *p*-Dimethylaminobenzhydrol (1 g.) in 10 c.c. of dilute hydrochloric acid (1·1 mols.) was added to *p*-toluenesulphinic acid (0·9 g.) in water (60 c.c.). After 2 hours at 20° the sulphone had crystallised in quantitative yield (for m. p. and analysis, see Table).

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169. *Alkyl–Oxygen Fission in Carboxylic Esters. Part IV.*

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Esters of optically active anisyl-1-naphthylcarbinol and anisylmethylcarbinol react, with racemisation, with carboxylic acids and with alcohols. When the hydrogen phthalates of these alcohols are hydrolysed by dilute aqueous alkali racemisation occurs, but optical purity is maintained on hydrolysis by concentrated alkali in alcoholic solution. From aqueous solutions of sodium salts of the optically active hydrogen phthalates, half-racemised neutral esters separate; in the presence of sodium *p*-toluenesulphinate, the sodium salts are converted into racemic sulphones. The hydrogen succinate of anisyl-1-naphthylcarbinol undergoes similar reactions. These reactions are similar to those described in Parts I (*J.*, 1942, 556), II (*J.*, 1942, 605), and III (previous paper).

The dependence of alkyl–oxygen fission on electron-release in the carbinol radical, stability of the anion, and ionising power of the medium is surveyed. The solubility of acid esters in dilute alkaline media is a factor which makes the occurrence of alkyl–oxygen fission, during alkaline hydrolysis, more common in acid than in neutral esters.

(+)ANISYLNAPHTHYLCARBINOL is obtained *via* fractional crystallisation of the brucine salt of the *dl*-hydrogen phthalate or succinate, and (+)anisylmethylcarbinol similarly from the cinchonidine salt of the *dl*-hydrogen phthalate. The reactions of the hydrogen phthalate and succinate of these carbinols, which are exactly analogous to those of *p*-methoxybenzhydrol (Part II, *loc. cit.*) and other carbinols (Part III, *loc. cit.*), are described below, and need little further discussion. To four points, brief reference is desirable. (i) The neutral phthalate (*lævo*-anisyl-1-naphthylcarbinyl phthalate), deposited from a solution of (−)anisyl-1-naphthylcarbinyl hydrogen phthalate in one molecular proportion of aqueous sodium hydroxide, is obtained in crystalline form, as were those of *p*-methoxy-*p'*-methyl- and p-methoxy-*p'*-*iso*propyl-benzhydrols (Part III, *loc. cit.*) [the neutral phthalate originally prepared by this method (that of *p*-methoxybenzhydrol, Part II, *loc. cit.*) did not crystallise].

(ii) The *dl*-neutral phthalate is formed from the (−)hydrogen phthalate in chloroform solution, with deposition of phthalic acid. This complete racemisation is in contrast to the half-racemisation which occurs when the neutral phthalate is deposited from aqueous solution. In chloroform, the neutral ester remains dissolved, and there is a continued interchange of anisylnaphthylcarbinol kations, leading to complete racemisation; from aqueous solution it separates when only half the anisylnaphthylcarbinol groups have undergone racemisation.

(iii) A half-racemised *laevo*-neutral succinate is obtained from the (−)hydrogen succinate of anisyl-1-naphthylcarbinol, in the same way as the *laevo*-neutral phthalate.

(iv) The α-methyl group in anisylmethylcarbinol enables its kation to decompose to an olefin. *p*-Methoxystyrene is formed from the carbinol on heating (or slowly at room temperature) and also during hydrolysis of the hydrogen phthalate (by steam-distillation from alkaline solution) under conditions where alkyl–oxygen fission occurs.

1 : 1′ Di-*p*-methoxyphenyldiethyl ether is also formed under the above conditions, presumably by interaction of carbinol molecules with anisylmethylcarbinol kations. Corresponding ethers are formed on heating *p*-methoxybenzhydryl- or anisylnaphthyl-carbinol, but were not observed in the products of hydrolysis of their hydrogen phthalates, possibly because the carbinols crystallised rapidly from the warm alkaline solutions, thus avoiding the prolonged heating of steam-distillation.

It is convenient to summarise the general conclusions so far drawn in these investigations (on the particular points of the mechanisms of the neutral ester and sulphone formations, we are not yet able to add to the discussion given in Part II, *loc. cit.*).

With regard to the reactions of esters with acids or alcohols :

(i) The reactivity of the esters decreases as electron-availability at the carbinol carbon atom decreases, the order in terms of the carbinols from which the esters are derived being : (*a*) Anisyl-1-naphthylcarbinol, *p*-methoxybenzhydrol, and other *p*-alkoxyarylcarbinols, roughly in order of electron release from the substituent groups (see Parts II, III, V). (*b*) Anisyl alcohol (see Part III). (*c*) α- and γ-Substituted allyl alcohols (see Part I). (*d*) 1-Naphthylmethylcarbinol, and *o*-chloro- and *m*-methoxy-benzhydrol (see Part III). (*e*) Phenylmethylcarbinol (see Part III).

(ii) The solvent-reactants can be arranged in order of decreasing reactivity: formic acid > acetic acid > ethyl or methyl alcohol. Some esters which do not react with anhydrous solvents do so when water is added to the solution (Part III).

(iii) Increase in ease of separation of the anion favours the reaction. Thus the *p*-toluenesulphinate of phenylmethylcarbinol reacts with anhydrous acetic acid (*J.*, 1933, 173) while its hydrogen phthalate does not (compare *K* of toluenesulphinic acid, *ca.* 10^{-2}; first *K* of phthalic acid, *ca.* 10^{-3}).

(iv) The above observations agree with the suggested unimolecular mechanism (Part I), the ionisation of the ester being promoted by electron-release in the carbinol radical, by stability of the anion, and by the dissociating effect of the solvent. When these factors result in alkyl–oxygen fission, a state of equilibrium is set up, and the reaction is forced to completion in accordance with the mass-action principle; in our experiments there is usually excess of one reactant (*e.g.*, acid or alcohol), and one product (*e.g.*, phthalic acid) separates from the solution.

With regard to alkaline hydrolysis, our results are complementary, not contradictory, to previous investigations in which alkyl–oxygen fission was found not to occur. The most relevant case is that of Ingold and Ingold (*J.*, 1932, 756), who found that rearrangement did not occur in the hydrolysis of α-methylallyl acetate by 0·2N-sodium hydroxide. This ester is less likely to react by alkyl–oxygen fission than the esters of the αγ-disubstituted allyl alcohols which we described in Part I (see Balfe, Hills, Kenyon, Phillips, and Platt, *J.*, 1943, 348), and the medium used by Ingold and Ingold contained a higher concentration of hydroxyl ions than the weak alkalis found to promote alkyl–oxygen fission in esters of the substituted allyl alcohols. It is to be observed that our experiments, as yet, have been confined to the hydrolysis of acid esters, in which the main effect of weak alkalis is to bring the ester into solution in an ionising medium (water) in which the concentration of free hydroxyl ions is not high, but from which the carbonium kation can extract hydroxyl ions. Thus, as Day and Ingold (*Trans. Faraday Soc.*, 1941, **37**, 686) pointed out, the hydrolysis with " weak alkali " is in effect hydrolysis in neutral solution. Ionisation of the free carboxyl group, though necessary in the above scheme, does not in itself promote alkyl–oxygen fission, but must act against it, though, as the results show, does not prevent it. The point is discussed in more detail by Arcus and Kenyon (*J.*, 1938, 1912), though the suggestion there made, that in weakly alkaline solutions the hydrogen phthalates dissolve partly in the un-ionised form, cannot be upheld. In both strong and weak alkali (*i.e.*, at any pH value above about 7·5) the acid ester can only be present as an anion, and the different results obtained with alkaline solutions of different strengths must be ascribed to variations in their hydroxyl-ion concentrations. These variations are the controlling factor in the hydrolysis of esters in which there is a moderate tendency to alkyl–oxygen fission (*e.g.*,, substituted allyl esters), but is less important when the tendency to this mechanism is strong (*e.g.*, in *p*-alkoxybenzhydryl esters); in this case alkyl–oxygen fission occurs even when the concentration of hydroxyl ions is high, and can only be suppressed by reducing the ionising power of the solvent (*e.g.*,, replacing water by ethyl alcohol).

These considerations need not apply to the hydrolysis of esters of monobasic acids, which is commonly brought about by strong alkali, which favours acyl–oxygen fission because of the high concentration of hydroxyl ions. It is also possible that when the ester remains as a separate phase the hydrolysis is initiated by attack of hydroxyl ions, on surface ester molecules, a bimolecular process favouring acyl–oxygen fission. When the ester is brought into solution by addition, *e.g.*, of ethyl alcohol, the alkyl–oxygen mechanism is again retarded because the ionising power of the medium is diminished.

Experimental.

dl-Anisyl-1-naphthylcarbinol (prepared by Grignard reaction) has m. p. 87° (Shurakowski, *J. Russ. Phys. Chem. Soc.*, 1909, **41**, 1692, gives m. p. 87°). A mixture of the carbinol (26·5 g.), powdered phthalic anhydride (15 g.), benzene (30 c.c.), and pyridine (10 c.c.), brought to solution by gentle warming then left 3 days at room temperature (development of yellow colour indicates decomposition), yielded the *dl*-phthalate, which, recrystallised from benzene–light petroleum and then from benzene, was obtained in prisms, m. p. 151° (40 g.) (Found, by rapid titration with 0·1N-sodium hydroxide : *M*, 410. Calc. for $C_{26}H_{20}O_5$: *M*, 412). From acetone the phthalate separated with 1 mol. of solvent, m. p. 85° (Found : equiv., 471. Calc. for $C_{26}H_{20}O_5,C_3H_6O$: equiv., 470). A solution of these crystals in ethyl alcohol yielded the 2 : 4-dinitrophenylhydrazone of acetone, m. p. and mixed m. p. 128°. The m. p. of these crystals slowly rose and after 10 weeks was 151°. From the phthalate (104 g.) and brucine (117 g.) in a mixture of acetone (100 c.c.) and ethyl acetate (200 c.c.) after 2 days a brucine salt separated. After 4 recrystallisations from acetone–ethyl acetate, this yielded brucine (−)anisyl-1-naphthylcarbinyl phthalate (100 g., m. p. 129—130°, decomp.) from which the (−)hydrogen phthalate was obtained as crystalline powder, m. p. 62—63° (Found : *M*, 415). Rotatory powers are in Table I.

The (−)hydrogen phthalate rapidly racemised in solution; in the solid state it slowly changed to a gummy mass, with extensive racemisation, and was then largely neutral phthalate.

(−)*Anisyl-1-naphthylcarbinol.*—From the (−)phthalate (2 g., $[\alpha]_{5893}$ −58° in carbon disulphide) in ethyl alcohol

(120 c.c.) by sodium hydroxide (0·5 c.c. of 50%). M. p. 113—114°. Recrystallised from ether–light petroleum, it had m. p. 114—115° [1·1 g., bulky clusters of needles, $[\alpha]_{5893}$ −60·5° in carbon disulphide (*l*, 2; *c*, 1·5)]. Hydrolysis of the (−)phthalate with 10N-sodium hydroxide (excess) gave a *laevo*-carbinol, m. p. 80—96°, $[\alpha]_{5893}$ −29·2° (*l*, 2; *c*, 1·0 in carbon disulphide); 0·3N-sodium carbonate (excess) gave a carbinol with $[\alpha]_{5893}$ −14·4° (*l*, 2; *c*, 1·0 in carbon disulphide), m. p. 72—83°. From the mother liquors from recrystallisation of the above brucine salt, a *dextro*-carbinol was obtained, m. p. 73—76°, $[\alpha]_{5893}$ +42° in carbon disulphide. Twice recrystallised from ether–light petroleum, it had m. p. 114—115°, $[\alpha]_{5893}$ +60·2° (*l*, 2; *c*, 1·5 in carbon disulphide). The *dl*-carbinol, m. p. 87°, crystallised from the ether–light petroleum filtrate.

dl-1-*Naphthylcarbinyl Hydrogen Succinate*.—Prepared in the same way as the phthalate, this formed clusters of prisms, m. p. 125° (Found: *M*, 362. Calc. for $C_{22}H_{20}O_5$: *M*, 364). Its brucine salt, prepared in, and thrice recrystallised from, the minimum of acetone, yielded the salt of the (+)succinate (39 g. from 36 g. of *dl*-hydrogen succinate), m. p. 122—123° (decomp.). From this salt the (+)hydrogen succinate (12 g.), m. p. 55—57°, was obtained as an oil which solidified, and was ground and dried in a vacuum. Rotatory powers are in Table II. The more soluble fraction of the brucine salt gave a *laevo*-hydrogen succinate (23 g.) the cinchonidine salt of which, thrice recrystallised from acetone, yielded the cinchonidine salt of (−)-anisyl-1-naphthylcarbinyl hydrogen succinate (30 g. irregular prisms, m. p. 160°). From this salt (−)*anisyl-1-naphthylcarbinyl hydrogen succinate* (15 g.) was obtained; $[\alpha]_{5893}$ −49·9° in benzene (*l*, 2; *c*, 1), m. p. 53—55° (Found: *M*, 386. $C_{22}H_{20}O_5$ requires *M*, 364).

The (+) and (−)hydrogen succinates, on hydrolysis with alcoholic sodium hydroxide (see above) yielded respectively (+) and (−)anisyl-1-naphthylcarbinols, both m. p. 114—115°. On hydrolysis with 5N-sodium hydroxide, the (+)hydrogen succinate yielded carbinol with $[\alpha]_{5893}$ +25·5° in carbon disulphide (*l*, 2; *c*, 1·0), m. p. 76—89°.

dl-*Anisyl-1-naphthylcarbinyl phthalate* was prepared from the acid ester in aqueous sodium hydroxide. From a solution of the *dl*-ester (10 g.) in 81 c.c. of 0·3N-sodium hydroxide, the neutral *ester* crystallised (7·8 g.; calc., 8·0 g.). It recrystallised from benzene–*cyclo*hexane in clusters of small nodules, m. p. 127—128° (decomp.) (Found: C, 79·7; H, 5·6; equiv., 326. $C_{44}H_{34}O_6$ requires C, 80·2; H, 5·2%; equiv., 329. Further recrystallisation did not give a product of better analysis). The aqueous filtrate yielded phthalic acid (1·85 g.; calc., 2·0 g.). From the (−)hydrogen phthalate (2·0 g., $[\alpha]_{5893}$ −58·0° in carbon disulphide) the *laevo*-neutral ester (1·6 g.) crystallised, $[\alpha]_{5893}$ −24·6° (in carbon disulphide). This ester (0·8 g.) on hydrolysis with 0·5 c.c. of 50% sodium hydroxide in 120 c.c. of ethyl alcohol, gave a *laevo*-carbinol, m. p. 72—76° with $[\alpha]_{5893}$ −29·2° (*l*, 2; *c*, 1·5) in carbon disulphide, *i.e.*, approximately half the rotatory power of the optically pure carbinol.

Similarly, anisyl-1-naphthylcarbinyl succinate separated from a solution of the acid ester (7·3 g., $[\alpha]_{5893}$ −50·2° in benzene) in aqueous sodium hydroxide (67 c.c.; 0·3N) (5·7 g.; calc., 6·1 g.). It crystallised with difficulty, m. p. 57—58°, $[\alpha]_{5893}$ −28·0° in benzene (*l*, 2; *c*, 1·00) (Found: equiv., 298. Calc. for $C_{40}H_{34}O_6$: equiv., 304). This neutral ester (4 g.) was warmed on the steam-bath for 3 minutes with sodium hydroxide (1 c.c. of 50%) in 200 c.c. of ethyl alcohol. On dilution with water, the carbinol (3 g.) crystallised, m. p. 70—73°, $[\alpha]_{5893}$ −28° (*l*, 2·0; *c*, 1·5) in carbon disulphide, *i.e.*, approximately half-racemised. This carbinol, by one recrystallisation from ether–light petroleum, was separated into approximately equal amounts of (−)carbinol (needles, m. p. 112—113°, $[\alpha]_{5893}$ −58° in carbon disulphide) and almost racemic carbinol (prisms, m. p. 87°).

Dismutation of the Hydrogen Phthalate of Anisyl-1-naphthylcarbinol.—From the *dl*-hydrogen phthalate (8·25 g.), heated under reflux in dry chloroform (30 c.c.) for several hours, phthalic acid (1·6 g.; calc., 1·7 g.) separated. On evaporation of the filtrate, trituration of the residue with light petroleum, and crystallisation from benzene–*cyclo*hexane, the neutral phthalate (m. p. 127—128°) was obtained (6·45 g.; calc., 6·6 g.). From a solution of the (−)hydrogen phthalate (4·2 g.) in chloroform, after 48 hours at room temperature, phthalic acid and the *dl*-neutral phthalate, m. p. 122—123° (3·1 g.; calc., 3·3 g.) were obtained in a similar way.

p-*Tolyl Anisyl-1-naphthylmethyl Sulphone*.—A solution of the *dl*-hydrogen phthalate (4·1 g.) in sodium hydroxide (34 c.c. of 0·3N) was filtered rapidly into a solution of sodium *p*-toluenesulphinate (2·2 g.) in water (50 c.c.). After 2 days, the crystalline mass of dl-*sulphone* was removed, washed, and dried (3·9 g.; calc., 4·0 g.). Twice recrystallised from water it was obtained in prisms, m. p. 141° (Found: S, 8·1. $C_{25}H_{22}O_2S$ requires S, 8·0%). The filtrate yielded phthalic acid (1·6 g.; calc., 1·7 g.).

From the (−)hydrogen phthalate, and the *dl*- and (+)hydrogen succinate, the *dl*-sulphone, m. p. 141°, was obtained.

Anisyl-1-naphthylmethyl Ethyl Ether.—The *dl*-hydrogen phthalate (4·1 g.) was heated under reflux in ethyl alcohol (200 c.c.) for 6 hours. On cooling, the ethyl ether (2·1 g.) crystallised; a further 0·75 g. (total, 2·85 g.; calc., 2·9 g.) was obtained from the filtrate together with phthalic acid (1·65 g.; calc., 1·7 g.). The dl-*ethyl ether* crystallised from ethyl alcohol in flat rhombs, m. p. 61° (Found: C, 82·4; H, 7·0. $C_{20}H_{20}O_2$ requires C, 82·2; H, 7·0%). The *dl*-ether was similarly obtained from the (−)hydrogen phthalate, the *dl*- and *laevo*-neutral phthalates, and the *dl*- and (+)-hydrogen succinates.

dl-*Anisyl-1-naphthylmethyl methyl ether* (rhombs, m. p. 50°) was obtained similarly from the (−)acid phthalate and succinate or *laevo*-neutral phthalate and succinate in methyl alcohol (Found: C, 81·6; H, 6·5. $C_{19}H_{18}O_2$ requires C, 82·0; H, 6·5%).

dl-*Dianisyl-1-naphthylmethyl Ether*.—The *dl*-carbinol (4 g.) was heated at 200° for 3 hours. Unchanged carbinol (2·6 g., m. p. 87°) was removed by trituration with warm ether. The residue (1·2 g., m. p. 152—154°) after three recrystallisations from benzene–ether yielded the *ether* as clusters of prisms, m. p. 160—161° (Found: C, 84·9; H, 5·8. $C_{36}H_{30}O_2$ requires C, 84·7; H, 5·9%).

dl-*Anisyl-1-naphthylmethyl Chloride*.—The *dl*- and the (+)-carbinol were immediately converted into the *dl*-chloride by trituration with cold concentrated hydrochloric acid. The chloride did not crystallise; it dissolved in warm light petroleum and separated on cooling as a colourless oil (Found by titration with N-sodium hydroxide: *M*, 277. Calc. for $C_{18}H_{15}OCl$: *M*, 282·5). From a solution of the chloride (2·5 g.) in ethyl alcohol (20 c.c.), on evaporation at room temperature, the *dl*-ethyl ether (2·5 g., m. p. 61°) crystallised.

dl-Anisylmethylcarbinol (88% yield), from methylmagnesium bromide (1 mol.) and anisaldehyde (110 g.; 0·8 mol.) at 0° (the complex being decomposed with ice and ammonium chloride), has b. p. 140—141°/17 mm., $n_D^{24°}$ 1·531. Klages (*Ber.*, 1903, **36**, 3592) gives n_D 1·537. The residue from distillation of the carbinol yields 1 : 1′-di-*p*-methoxyphenyldiethyl ether (3 g.), m. p. 51°.

TABLE I.

Specific Rotatory Powers of (−)*Anisyl-1-naphthylcarbinyl Hydrogen Phthalate in Various Solvents* (*l*, 2; *c*, 1·00).

Solvent.	*t*.	λ_{6438}.	λ_{5893}.	λ_{5780}.	λ_{5461}.	λ_{4358}.	λ_{4358}.
Carbon disulphide	17·2°	−20·4°	−58°	−66·7°	−77·1°	−120°	−131·0°
Benzene	17·2	−16·00	−32·2	−33·5	−41·1	− 58	− 65
Dioxan	17·2	− 4·3	−10·9	−12·1	−14·0	− 22	− 24·0

TABLE II.

Specific Rotatory Powers of (+)Anisyl-1-naphthylcarbinyl Hydrogen Succinate in Various Solvents (l, 2; c, 1·0).

Solvent.	*t.*	λ_{6438}.	λ_{5893}.	λ_{5780}.	λ_{5461}.	λ_{4800}.	λ_{4358}.
Benzene	20°	+39·0°	+50·1°	+53·2°	+62·4°	+87·3°	+112·1°
Chloroform	20	+29·0	+33·2	+35·5	+40·2	+50·0	+ 70·3
Ethanol	20	+26·0	+30·1	+31·5	+37·6	+48·0	+ 65·2

TABLE III.

*Specific Rotatory Powers of (+)Anisyl-1-naphthylcarbinol * in Various Solvents (l, 2).*

Solvent.	*c.*	*t.*	λ_{6438}.	λ_{5893}.	λ_{5780}.	λ_{5461}.	λ_{4800}.	λ_{4358}.
Carbon disulphide	1·50	18°	+48·3°	+60·9°	+64·5°	+74·8°	+ 90·8°	+149·6°
Ethanol	1·51	17·5	−24·8	−31·5	−33·1	−37·1	− 50·2	− 70·4
Ether	1·50	17·5	−49·9	−64·3	−66·6	−78·6	−113·9	−162·4

* We define as (+), the carbinol obtained from the (+)hydrogen phthalate and succinate.

Decomposition of the carbinol with formation of *p*-methoxystyrene (approx. 10%) and 1 : 1′-di-*p*-methoxyphenyldiethyl ether (approx. 20%) occurs (i) if during the Grignard reaction the temperature rises above 0°, (ii) if during isolation of the carbinol temperatures above 60° are used, (iii) on heating the pure carbinol on the steam-bath (1 hour), (iv) when the pure carbinol is kept at room temperature for 30 months.

p-Methoxystyrene has b. p. 84—87°/12 mm., $n_D^{24.5°}$ 1·5569. Klages (*loc. cit.*) gives n_D 1·5642. It yields 1 : 2-*dibromo*-1-p-*methoxyphenylethane* (1 : 2-dibromo-1-anisylethane), needles, m. p. 80° (decomp.) from ether–light petroleum (Found : Br, 53·8. $C_9H_{10}Br_2$ requires Br, 54·4%).

1 : 1′-*Di*-p-*methoxydiphenyldiethyl ether* crystallises from aqueous acetone or methyl alcohol in needles, m. p. 51°, b. p. 212°/16 mm. (Found : C, 75·5; H, 8·0. $C_{18}H_{12}O_3$ requires C, 75·5; H, 7·7%).

dl-Anisylmethylcarbinyl hydrogen phthalate (from the alcohol, b. p. 131—133°/13 mm., phthalic anhydride, and pyridine, 1 mol. of each at 50° for 30 minutes, then decomposed with hydrochloric acid) formed short needles (m. p. 86—87°), from carbon disulphide or ether–light petroleum (yield 90%) (Found, by rapid titration with NaOH : *M*, 295. Calc. for $C_{17}H_{16}O_5$: *M*, 300). Phthalic acid was deposited from solutions of the phthalate in chloroform, methyl alcohol, or ethyl alcohol. The cinchonidine salt (needles, m. p. 150—152°) from the *dl*-phthalate and cinchonidine, in acetone, separated as the salt of the *laevo*-phthalate; decomposed with hydrochloric acid it gave *laevo*-phthalate, from which the (−)phthalate, irregular prisms, m. p. 110—115° (Found : *M*, 301), was obtained after three recrystallisations from methylene chloride–light petroleum (from the mother liquors, only *dl*-phthalate was obtained). From the more soluble fraction of the cinchonidine salt, the (+)phthalate was obtained in a similar way, m. p. 110—115° (Found : *M*, 302). Rotatory powers are in Table IV. The above procedure is quicker and more efficient than resolution by fractional crystallisation of the cinchonidine or brucine salts.

From the (+)hydrogen phthalate, the (+)carbinol was obtained on hydrolysis (9 g. of phthalate, 3 g. of sodium hydroxide, 50 c.c. of ethyl alcohol, 15 c.c. of water; one hour on steam-bath, followed by dilution with water, extraction of the liberated alcohol with ether, and subsequent distillation), b. p. 140—142°/23 mm. Rotatory powers of the (+)carbinol are in Table V.

On hydrolysis of the (+)phthalate with 3N-sodium hydroxide, some racemisation occurred, the alcohol having $a_{5461}^{20°}$ +26·4° (*l*, 0·5); with more dilute aqueous alkali, the amount of racemisation increased, and some *p*-methoxystyrene and di-*p*-methoxyphenyldiethyl ether were formed.

TABLE IV.

Specific Rotatory Powers of Anisylmethylcarbinyl Hydrogen Phthalate in Various Solvents (20°).

Solvent.	*c*, g. per 100 c.c.	λ_{6438}.	λ_{5893}.	λ_{5780}.	λ_{5461}.	λ_{4358}.
		(−)*Phthalate.*				
Carbon disulphide	0·101	—	−50°	−74°	−79°	−198°
Pyridine	5·005	−26·5°	−30·5	−37·9	−39	− 62
Benzene	1·195	−23·0	−30·5	−37·2	−37·6	− 69
Acetic acid	5·000	—	−20·9	—	−23·7	− 40·5
Methylene chloride	5·011	−12·8	−14·6	−15·7	−16·4	− 24·3
Methyl alcohol	5·001	+11·2	+15·2	+18·2	+19·0	+ 44·8
Ethyl alcohol	5·000	+17·5	+21·5	+22·1	+26·9	+ 59·0
		(+)*Phthalate.*				
Chloroform	4·390	+10·0	+12·1	+12·4	+14·5	+ 15·4
Ethyl alcohol	5·429	−17·7	−23·0	−23·2	−29·0	− 66·8

* We define as (+), the hydrogen phthalate which yields (+)carbinol (Table V) on hydrolysis.

TABLE V.

Observed Rotatory Powers of (+)Anisylmethylcarbinol at Different Temperatures (l, 0·5).

t.	15·0°.	28·25°.	32·25°.	45·0°.	60·5°.
λ 5780	+29·26°	+28·25°	+27·76°	+27·09°	+25·78°
λ 5461	33·54	32·36	31·71	30·88	29·47
λ 4358	60·40	58·00	56·90	55·55	52·55

$d_4^{19.5°}$ 1·079, $d_4^{34.5°}$ 1·065, $d_4^{45.5°}$ 1·051, $d_4^{60°}$ 1·044

Using a different specimen of the (+)alcohol, the following values were obtained (*l*, 0·5; *t*, 20·0°) :

λ	6438	5893	5780	5461	5086	4800	4358
a	+22·05°	+27·18°	+28·48°	+33·31°	+38·85°	+44·53°	+58·80°

dextro-1-*Anisylethyl Methyl Ether*.—A solution of (+)anisylmethylcarbinyl hydrogen phthalate (5 g. with $[\alpha]_{5461}$ −21·8° in ethyl alcoholic solution) in anhydrous methyl alcohol (30 c.c.) was kept overnight and then slowly evaporated on the steam-bath. The partly crystalline residue was separated by extraction with chloroform into phthalic acid (2·4 g.) and dextro-1-*anisylethyl methyl ether* (2 g.), b. p. 116—117°/23 mm., $n_D^{24°}$ 1·505; $\alpha_{5893}^{20°}$ +0·14°; $\alpha_{5461}^{20°}$ +0·13; $\alpha_{4358}^{20°}$ +0·33 (*l*, 0·25) (Found: C, 72·3; H, 8·6. $C_{10}H_{14}O_2$ requires C, 72·3; H, 8·5%).

Action of Glacial Acetic Acid on (−)*Anisylmethylcarbinyl Hydrogen Phthalate*.—The rotatory power of a 5% solution of the (−)phthalate in glacial acetic acid (Table I) fell to half its value after 10 hours at room temperature and had become zero after 10 days. From the solution (which originally contained 5 g. of phthalate) there were obtained phthalic acid (2·4 g.) and *dl*-anisylmethylcarbinyl acetate (2 c.c.), b. p. 137°/15 mm., $n_D^{17°}$ 1·519 (Found: *M*, 192. Calc. for $C_{11}H_{14}O_2$: *M*, 194).

Action of Dilute Aqueous Sodium Hydroxide on (−)*Anisylmethylcarbinyl Hydrogen Phthalate*.—A filtered solution of the (−)acid ester (12 g., $[\alpha]_{5893}$ −20·2° in ethyl alcohol) in sodium hydroxide (140 c.c. of 0·3N) after being kept overnight had deposited a viscous oil. This was triturated with ethyl alcohol in order to remove traces of anisylmethylcarbinol, and dried (3·1 g.); it had $\alpha_{5893}^{17°}$ −4·3° (*l*, 0·5) (Found: *M*, 412. Calc. for $C_{26}H_{26}O_6$: *M*, 434).

On hydrolysis with 2·5 mols. of 5N-sodium hydroxide, this neutral ester yielded the alcohol (2·2 g.), b. p. 125—126°/10 mm., $n_D^{17·5°}$ 1·534, $\alpha_{5893}^{17·5°}$ −8·4° (*l*, 0·5).

dl-p-*Tolyl* 1-*Anisylethyl Sulphone*.—A solution of the hydrogen phthalic ester (3·0 g., $[\alpha]_{5893}^{20°}$ −18° in ethyl alcohol) in sodium hydroxide (35 c.c. of 0·3N) was filtered into a solution of sodium *p*-toluenesulphinate (2·15 g.) in water (25 c.c.). The solution rapidly turned cloudy and crystalline dl-p-*tolyl* 1-*anisylethyl sulphone* began to separate. After several days this (1·6 g.) was removed by filtration; it was optically inactive in chloroform solution and separated from ethyl alcohol as a micro-crystalline powder, m. p. 119—120° (Found: S, 11·0. $C_{16}H_{18}O_3S$ requires S, 11·0%).

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170. *Alkyl–Oxygen Fission in Carboxylic Esters. Part V.*

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The resolution of *p*-phenoxybenzhydrol, and reactions of its hydrogen phthalate, similar to those recorded in previous papers, are described. The hydrogen phthalate in aqueous alkali has at room temperature less tendency, and at 80° more tendency, to alkyl–oxygen fission than has the hydrogen phthalate of *p*-methoxybenzhydrol. Homophthalates and diphenates of *p*-phenoxybenzhydrol are described.

The aralkylating action of some of the hydrogen phthalates which react by alkyl–oxygen fission is illustrated by their reactions with *p*-toluenesulphinic acid, thio-*p*-cresol, phenol, β-naphthol, and ammonia, giving the corresponding sulphones, thioethers, ethers, and amines. Some of the carbinols also are shown to give the sulphones and thioethers. The *O*-aralkylations of α-oxime salts and of the sodium salt of *p*-bromophenylnitromethane by reaction with the sodium salt of *p*-methoxybenzhydryl hydrogen phthalate are described.

THE (+)hydrogen phthalate of *p*-phenoxybenzhydrol, obtained by fractional crystallisation of the quinidine salt of the *dl*-phthalate, yields, on hydrolysis in alcoholic sodium hydroxide, (+)-*p*-phenoxybenzhydrol. The (+)carbinol is also obtained when the hydrolysis is conducted in the cold with N-sodium hydroxide, indicating that the tendency to acyl–oxygen fission is greater in this carbinol than in *p*-methoxybenzhydrol, which is largely racemised on aqueous hydrolysis of its phthalate. Similarly, (+)-*p*-phenoxybenzhydryl hydrogen phthalate can be recovered unchanged from solution in a slight excess of aqueous alkali, whereas under these conditions *p*-methoxybenzhydryl hydrogen phthalate yields the neutral ester. When warmed with a greater excess (2 mols. or more) of aqueous alkali, *p*-phenoxybenzhydryl hydrogen phthalate reacts by alkyl–oxygen fission, yielding the neutral diphthalate if the concentration of hydrogen phthalate is above 4%, and carbinol at low concentration (below 20 g./l.). At the lower concentrations, the probability of a liberated kation reacting with a molecule of hydrogen phthalate is decreased, and the probability of reaction with a water molecule or hydroxyl ion is, therefore, increased. In the case of *p*-methoxybenzhydryl hydrogen phthalate, on the other hand, increase in temperature or concentration of alkali results in some acyl–oxygen fission (retention of optical activity). These results indicate the dual capacity of the *p*-phenoxy-groups for electron attraction (which assists co-ordination of the hydroxyl group and so promotes acyl–oxygen hydrolysis in the cold), or for electron release (which in conjunction with thermal energy promotes some alkyl–oxygen fission on heating).

p-Phenoxybenzhydryl hydrogen phthalate yields, by methods previously described, the *p*-tolyl sulphone and the methyl and ethyl ethers: the methyl ether has also been obtained from the neutral phthalate on heating in methyl alcohol. The carbinol itself yields di-*p*-phenoxybenzhydryl ether on heating, and the chloride on warming with concentrated hydrochloric acid. These reactions in general occur less readily than with *p*-methoxybenzhydrol, and further evidence of a lesser tendency to alkyl–oxygen fission in the *p*-phenoxybenzhydrol is given by the formation of the acetate (instead of the chloride, cf. Part II) on reaction with acetyl chloride.

Neutral di-esters of diphenic and homophthalic acids have been obtained on warming the corresponding acid esters of *p*-phenoxybenzhydrol and anisyl-1-naphthylcarbinol in a slight excess of aqueous sodium hydroxide, and from the acid esters of *o*-methoxyphenyl-1-naphthylcarbinol in the cold. Also a *p*-tolyl sulphone was obtained from the acid diphenate of *p*-phenoxybenzhydrol.

In general, the reactions of esters of benzhydrol and related carbinols may be summarised by describing

them as effective aralkylating agents, the reactions proceeding to completion on account of the precipitation of one or other product from the reaction mixtures. This is further illustrated by the reactions of a number of the hydrogen phthalates in chloroform solution (see experimental section) with *p*-toluenesulphinic acid, thio-*p*-cresol, phenol, or β-naphthol to give the corresponding sulphones, thioethers, or ethers. The hydrogen phthalate of *p*-methoxybenzhydrol (at room temperature) and of anisyl-1-naphthylcarbinol and *p*-phenoxybenzhydrol (at 100°) react with concentrated aqueous ammonia to give the substituted benzhydrylamines: those of benzhydrol and anisyl alcohol, on account of their lesser tendency to alkyl–oxygen fission, only undergo hydrolysis to the carbinol, slowly at room temperature, and more rapidly on heating. In aqueous ammonia, the concentration of hydroxyl ions is low compared with that of ammonia (or solvated ammonia) molecules, with which the *p*-substituted benzhydryl kations, therefore, preferentially react to give the amines. In aqueous methylamine, with which *p*-methoxybenzhydryl hydrogen phthalate reacts to give the benzhydrol, the concentration of hydroxyl ions is higher, and the amine is to a large extent present in the form of $MeNH_2^{\oplus}$, carrying a charge which will diminish interaction with benzhydryl kations: these, therefore, react preferentially with the hydroxyl ions.

The aralkylating action of the *p*-methoxybenzhydryl phthalic ester is also shown by its reaction (*i.e.*, in the presence of a slight excess of sodium hydroxide) with the sodium salts of α-oximes (*o*-methoxybenzaldoxime and *p*-nitrobenzaldoxime) to give *O*-oxime ethers (cf. Brady, Dunn, and Goldstein, *J.*, 1926, 2386) on *O*-alkylation of α-oximes by methyl sulphate. An *O*-ether of *o*-methoxybenzaldoxime has also been obtained from the hydrogen phthalate of *o*-methoxyphenyl-1-naphthylcarbinol. The sodium salt of *p*-methoxybenzhydryl hydrogen phthalate reacts with cupferron, giving a compound which is presumably one of the two possible *O*-ethers,* and with the sodium salt of *p*-bromophenylnitromethane, giving the nitronic ester by *O*-alkylation (cf. Arndt and Rose, *J.*, 1935, 1, on *O*-alkylation of *aci*-nitro-compounds).

In the reactions in chloroform solution, the phthalate ionises (involving the first dissociation of phthalic acid, K, $1{\cdot}3 \times 10^{-3}$) and the kation displaces a hydrogen ion from the reactant. In aqueous sodium hydroxide, the second dissociation of phthalic acid (K, $3{\cdot}1 \times 10^{-6}$) is involved, and the kation reacts with another benzhydryl phthalate anion to give the neutral ester, or with a water molecule to give the hydrol, according to the relative concentrations. Though the separation of the products takes several hours, the reactions are probably very rapid (see Part I). If anions (*e.g.*, of hydroxyl, sulphinate, oxime salt, or of *aci*-nitro-compound) or molecules (ammonia) of high co-ordinating power are present, or if anions (*e.g.*, bivalent phthalate anion; Part I) are present in high concentration, the reaction is diverted to these. There are two anomalous cases: *p*-substituted benzhydryl benzoate is not formed when sodium benzoate is present in equimolar concentration (Part I) or in five-molar excess (subsequent experiments), and a mixed phthalic ester is not formed when octyl hydrogen phthalate is present in five-molar excess (Part I: the observation there given, that the neutral phthalate which is formed is racemic, is not anomalous; the neutral ester was not separated until 7 days after deposition, and it is shown in Part I that it racemises during this time). Though both the benzoate and the octyl phthalate anions might be described as not of high co-ordinating power, in the sense used above, they would be expected when present in excess to react in a similar way to the bivalent phthalate anion.

In aqueous sodium hydroxide, acid succinates of certain of these hydrols and carbinols (Part III and IV) react to give *p*-tolyl sulphones, as is to be expected from the similar strengths of the second dissociations of succinic (K, $2{\cdot}8 \times 10^{-6}$) and phthalic acids. Some neutral succinates are also formed, but there is a tendency for the hydrols to be formed from the succinates, under conditions where the phthalates give neutral esters. This may be related to the lower strength of the first dissociation of succinic acid (K, $6{\cdot}6 \times 10^{-5}$) compared with phthalic acid, resulting in a higher concentration of hydroxyl ions when acid succinates are dissolved in an equimolar amount of alkali, and, therefore, greater tendency of liberated kations to react with hydroxyl ions to give the hydrol or carbinol.

Some further reactions of the substituted benzhydrols and related carbinols (see experimental section), involving separation of the hydroxyl group, have been observed: the formation of sulphones on refluxing with *p*-toluenesulphinic acid in chloroform solution (see also Part III), and of thioethers with thio-*p*-cresol in the same solvent. Separation of water from the chloroform presumably drives these reactions to completion. In this connection mention should be made of the work of Fosse, who showed (*Compt. rend.*, 1907, **145**, 1291) that *C*-aralkylation of keto-methylene systems occurs when benzhydrol and its *p*-substituted homologues react in acid solution with, *e.g.*, acetoacetic ester or benzoylacetone, and formulated the reactions as involving removal of the hydroxyl groups of the hydrols, *i.e.*, alkyl–oxygen fission. Xanthhydrol was found by Fosse (*Compt. rend.*, 1912, **155**, 1019) to undergo this type of reaction with great ease—its structure must produce a very strong tendency to electron release—and he records the formation of its disulphide and peroxide on reaction with sodium sulphide and hydrogen peroxide respectively.

In Part III it is shown that anisyl alcohol and its hydrogen phthalate and acetate can react with alkyl–oxygen fission, though less readily than the benzhydrols, and this is further illustrated by reactions of the hydrogen phthalate with *p*-toluenesulphinic acid, thio-*p*-cresol, and ethyl alcohol. It also yields the neutral diphthalate when heated in chloroform solution (compare the formation of anisyl-1-naphthylcarbinyl diphthalate in chloroform solution, Part IV). Alkyl–oxygen fission, with resulting formation of neutral ester, occurs in chloroform solution when it involves ionisation of the first dissociation constant of phthalic acid, but not in

* Further examination of this substance, which might throw light on the structure of cupferron (Taylor and Baker, "Sidgwick's Organic Chemistry of Nitrogen," 1942, p. 456), has not yet been attempted.

aqueous sodium hydroxide (Part III), in which ionisation of the second carboxyl group would be involved (see Part IV).

p-Methoxybenzhydryl ether (Part II, *loc. cit.*) is very smoothly prepared by heating the hydrol with a solution of *p*-toluenesulphonic acid in water.

Experimental.

dl- *and* (+)-p-*Phenoxybenzhydrol and their Hydrogen Phthalates.*—*p*-Phenoxybenzophenone (m.p. 71°, from diphenyl ketone by Friedel–Crafts reaction; Kipper, *Ber.*, 1905, **38**, 2492) was reduced (100 g.) with powdered sodium hydroxide (100 g.) and zinc dust (100 g.) in ethyl alcohol by refluxing (3 hours). The solution was filtered and poured into ice-water. The precipitate, recrystallised from boiling ligroin, gave *p*-phenoxybenzhydrol, long silky needles, m. p. 76·5°. Overall yield, 130 g. of recrystallised hydrol from 100 g. of diphenyl ether. The hydrol (13·8 g.), phthalic anhydride (7·4 g.), and pyridine (7 g.) were heated at 60° for 6 hours, diluted with acetone, and poured slowly into excess of dilute hydrochloric acid at 0°. The oil was redissolved in acetone and reprecipitated with hydrochloric acid to remove excess of pyridine. The resulting solid hydrogen phthalate (20 g.; m. p. 138—139°) crystallised from most organic solvents as short needles, m. p. 143° (Found, on rapid titration with 0·1N-NaOH: *M*, 426. Calc. for $C_{27}H_{20}O_5$: *M*, 424). The hydrogen phthalate (85 g.) and quinidine (72 g.) were dissolved in warm acetone (250 c.c.); the salt which was deposited (102 g.) was recrystallised four times from acetone, yielding the quinidine salt of the (+)phthalate (42 g.), m.p. 137—138°. This was dissolved in warm acetone, and the (+)phthalate precipitated by iced hydrochloric acid: it was reprecipitated thrice in this way to remove all the quinidine; (+)-*p*-phenoxybenzhydryl hydrogen phthalate, clusters of short needles, m. p. 100—101° (*M*, as above, 426), had in benzene solution (*l*, 2; *c*, 2·553; *t*, 23°), $[\alpha]_{6708}$ + 8·0°, $[\alpha]_{5893}$ + 11·8°, $[\alpha]_{5780}$ + 12·2°, $[\alpha]_{5761}$ + 13·9°, $[\alpha]_{4358}$ + 28·3°, and in carbon disulphide (*l*, 2; *c*, 1·182; *t*, 20°), $[\alpha]_{5893}$ + 14·0°, $[\alpha]_{5780}$ + 16·9°, $[\alpha]_{5461}$ + 18·6°. The above solution in benzene after 70 days at room temperature had $[\alpha]_{5393}$ + 6·0°, and had deposited needles of almost pure *dl*-phthalate, m. p. 103—104°, $[\alpha]_{5893}$ + 0·6° in benzene (*l*, 2; *c*, 0·958).

The (+)hydrogen phthalate (2 g.) was warmed for a few minutes with sodium (2 g.) in 98% ethyl alcohol (60 c.c.). On dilution with water, (+)-*p*-phenoxybenzhydrol separated (1·25 g.); it recrystallised from carbon disulphide–ligroin in masses of long silky needles, m. p. 81—82°. In carbon disulphide (*l*, 2; *c*, 2·485; *t*, 19·5°) it had $[\alpha]_{5893}$ + 11·9°, $[\alpha]_{5780}$ + 13·7°, $[\alpha]_{5461}$ + 15·9°, $[\alpha]_{4358}$ + 31·4°. Hydrolysis of the (+)phthalate (1 g.) with 0·3N-sodium hydroxide (34 c.c.) at room temperature (2 days) gave the (+)hydrol with m. p. 81—82°, $[\alpha]^{20°}_{5893}$ (without previous recrystallisation), + 11·6° in carbon disulphide (*l*, 2; *c*, 1·91).

Reactions of p-*Phenoxybenzhydryl Hydrogen Phthalate with Aqueous Sodium Hydroxide.*—2—4 G. portions of hydrogen phthalate were used. The reaction conditions and products are summarised in the Table and further discussed in the notes below. *dl*-Phthalate was used except when otherwise stated.

	Molar ratio: NaOH/hydrogen phthalate.	Concn., g. hydrogen phthalate/l.	Temp.	Products. Neutral phthalate as % of maximum theoretical.	Other products.
1	1	125	20°	0	Sodium salt.
2	1·4	110	20 (after 3 weeks)	20	Unchanged hydrogen phthalate.
3	1·8	65	80	60	Hydrol (30%).
4	3	40	80	50	,,
5	6	25	80	60	,,
6	15	125	80	85	None
7	4·5	15	20	0	Hydrol (quantitative).
8	4	4	80	0	,, ,,

Expt. 1. Separation of the sodium salt as an oil or gum usually occurs when hydrogen phthalates (diphenates or homophthalates) of benzhydrols and related carbinols are dissolved in aqueous sodium hydroxide in high concentration (over 100 g./l.), and is encouraged by the presence of other sodium salts, *e.g.*, toluenesulphinate.

Expts. 3—6. Isolation of neutral ester and hydrol (compare Part II, *loc. cit.*). The gums which separated were washed with ethyl ether and water, dried, and extracted thrice with hot methyl alcohol (5-c.c. portions) followed by rapid cooling. The neutral ester separated and the hydrol was isolated from the methyl alcohol. A little ethyl ether was added to the neutral ester and the solvents removed under reduced pressure, leaving a glassy solid which softened at 47°. This was extracted with ligroin, dissolved in ether, and washed with alkali and with water, and the solvents were removed by distillation under reduced pressure at room temperature, leaving p-*phenoxybenzhydryl phthalate* as a glassy solid (Found: C, 81·2; H, 5·3. $C_{46}H_{34}O_6$ requires C, 80·9; H, 5·0%). Further evidence on the course of the reactions was obtained by drawing up balance sheets of (i) initial weight of hydrogen phthalate, (ii) alkali consumed in the reactions, (iii) yield of unchanged hydrogen phthalate (usually nil), (iv) neutral ester in crude gum, as determined by hydrolysis with 0·5N-sodium hydroxide, (v) alkali consumed in hydrolysis of phthalate to hydrol, from (i), (iii), and (iv). These calculations gave results agreeing with the determined weights of neutral ester and carbinol formed.

Expt. 4. From (+)hydrogen phthalate, the glassy, solid neutral ester had $[\alpha]^{20°}_{5893}$ + 17·7° in carbon disulphide (*l*, 2; *c*, 2·58). On hydrolysis with alcoholic potash it gave *dextro*-hydrol with $[\alpha]^{20°}_{5893}$ + 6·0° in carbon disulphide (*l*, 2; *c*, 2·69), *i.e.*, half the rotatory power of the (+)hydrol (cf. Part II, *loc. cit.*).

Reactions of p-*Phenoxybenzhydryl Hydrogen Phthalate.*—(i) 2·12 G. in 19 c.c. of 0·3N-sodium hydroxide, added to 1·8 g. of sodium *p*-toluenesulphinate in water (22 c.c.), did not react during 3 days at room temperature. After 15 minutes at 90°, p-*tolyl* p-*phenoxybenzhydryl sulphone* (2·1 g.) separated as prismatic needles, m. p. after recrystallisation from ethyl alcohol or acetic acid, 164—165° (Found: S, 7·7. $C_{26}H_{22}O_3S$ requires S, 7·7%). From (+)phthalate, *dl*-sulphone was obtained. (ii) (+)Phthalate (10 g.) in methyl alcohol (200 c.c.) was slowly distilled (4 hours). The residual oil was dissolved in ether and extracted with aqueous ammonia (which removed 3·8 g. of phthalic acid). The oil obtained from the ethereal solution had b. p. 207—210°/8 mm. (4·7 g.) and set to a crystalline mass of *dl*-*p*-phenoxybenzhydryl methyl ether, m. p. and mixed m. p. (see below), 27—28°. (iii) *dl*-Phthalate with ethyl alcohol as in (ii) above yielded 3·6 g. of phthalic acid and 7·0 g. of p-*phenoxybenzhydryl ethyl ether*, b. p. 227—228°/12 mm., which crystallised from ethyl alcohol in clusters of needles, m. p. 38—39° (Found: C, 82·6; H, 6·6. $C_{21}H_{20}O_2$ requires C, 82·9; H, 6·6%).

Di-*p*-phenoxybenzhydryl ether (3 g.) in methyl alcohol (70 c.c.), as in (ii) above, gave the *methyl ether* (2·1 g.) which, crystallised from methyl alcohol, had m. p. 27° (Found: C, 82·7; H, 6·3. $C_{26}H_{22}O_2$ requires C, 82·8; H, 6·2%).

Reactions of p-*Phenoxybenzhydrol.*—(iv) The hydrol (10 g.) was heated at 160° for 10 hours, then diluted with ethyl ether. The crystalline precipitate of *di*-p-*phenoxybenzhydryl ether* (4·1 g.; m. p. 175—190°) was soluble only in dioxan and *cyclo*hexane, and after many recrystallisations from the latter plus ether had m. p. 202° (Found: C, 85·2; H, 5·6. $C_{38}H_{30}O_3$ requires C, 85·4; H, 5·6%). (v) Hydrol (3 g.) was triturated with concentrated hydrochloric acid at 60°.

The chloride (3 g.) solidified on cooling; washed and dried (lime), it had m. p. 48—50°. Recrystallised from ligroin, it formed clusters of pale yellow needles, m.p. 49—50° (Norris and Blake, *J. Amer. Chem. Soc.*, 1928, **50**, 1809, give m. p. 49—50°) (Found, by reaction with excess of 0·1N-sodium hydroxide: *M*, 292. Calc.: *M*, 294). The chloride (1·5 g.) in benzene solution on shaking with water yielded the di-ether, m. p. and mixed m. p. (iv above) 201—202°. (vi) The hydrol (1 g.) was dissolved in acetyl chloride. After 2 hours at room temperature, the excess of acetyl chloride was removed under reduced pressure. The residual *p*-phenoxybenzhydryl acetate crystallised from ligroin in needles, m. p. 51—52° (Found, by hydrolysis with 0·1N-sodium hydroxide: *M*, 312. Calc. for $C_{21}H_{18}O_3$: *M*, 318). (vii) 3 G. of *dextro*-hydrol ($[\alpha]_{5893}^{18°}$ + 8·0° in carbon disulphide) by Einhorn's method gave 2·9 g. of *dextro*-benzoate, $[\alpha]_{5893}^{18°}$ + 28·9° in carbon disulphide (*l*, 2; *c*, 3·97). *dl*-Hydrol in the same way gave dl-*benzoate*, rosettes of needles, m. p. 61—62° (Found: C, 81·8; H, 5·4. $C_{26}H_{20}O_3$ requires C, 82·1; H, 5·3%).

p-Phenoxybenzhydryl hydrogen diphenate was prepared from the hydrol (13·8 g.), diphenic anhydride (11·2 g.), and pyridine (12 c.c.) warmed for 10 hours at 70°. The crude diphenate (22 g.) was purified by running a benzene solution into a column of magnesium oxide (activated by 4 hours' heating at 200°) then washing out with benzene containing 10% of ethyl alcohol. The first fraction of washings contained the hydrogen diphenate (2·5 g.), glassy solid, m. p. 150—151° (Found, by titration with 0·1N-sodium hydroxide: *M*, 498. Calc. for $C_{33}H_{24}O_5$: *M*, 500). By the usual methods, the hydrogen diphenate gave the *p*-tolyl sulphone (m. p. and mixed m. p. 163—164°) on heating the reactants at 90° for 30 minutes, and the neutral p-*phenoxybenzhydryl diphenate* (0·6 g. from 1·0 g. of hydrogen diphenate) on boiling the reactants for 10 minutes. The neutral ester was purified by the methods described under Expts. 3—6 above [Found: C, 82·5; H, 5·2; *M* (Rast), 730. $C_{52}H_{38}O_6$ requires C, 82·3; H, 5·0%; *M*, 758]. The following acid and neutral esters were prepared by exactly comparable methods:

	Temp. of prepn.	M. p.	Analysis.
p-Phenoxybenzhydryl hydrogen homophthalate	60°	140°	*M*, 434. Calc. for $C_{28}H_{22}O_5$: *M*, 438.
Di-*p*-phenoxybenzhydryl homophthalate	80	Oil	306 Mg. yielded 79 mg. of homophthalic acid (Calc.: 73 mg.).
o-Methoxyphenyl-1-naphthylcarbinyl hydrogen diphenate	60	135—136	*M*, 485. Calc. for $C_{32}H_{24}O_5$: *M*, 488.
o-Methoxyphenyl-1-naphthylcarbinyl diphenate	20	Glassy solid	2·0 G. gave 1·4 g. of carbinol and 0·6 g. of diphenic acid (Calc., 1·4 and 0·6 g.).
Anisyl-1-naphthylcarbinyl hydrogen homophthalate	50	133	*M*, 419. Calc. for $C_{27}H_{22}O_5$: *M*, 426.
Anisyl-1-naphthylcarbinyl homophthalate	20	Glassy solid	1 G. gave 0·75 g. of carbinol and 0·21 g. of acid (Calc., 0·62 and 0·21 g.).

Further Reactions of Hydrogen Phthalates.—Hydrogen phthalates of the following carbinols were used: (I) *p*-Methoxybenzhydrol (see Part II, but, contrary to the description therein, the preparation of the hydrogen phthalate is best conducted at room temperature over several days); (II) anisyl alcohol (see Part III); (III) *p*-phenoxybenzhydrol (see above); (IV) anisylmethylcarbinol (see Part IV); (V) (+)anisylnaphthylcarbinol (see Part IV). *p*-Tolyl sulphones were obtained by heating solutions of the hydrogen phthalates with *p*-toluenesulphinic acid (approx. equal weight) in chloroform, heating being continued for some time after separation of phthalic acid ceased (1—20 hours). *p*-Tolyl thioethers and phenyl ethers, and a 1-naphthyl ether, were obtained in exactly the same way with the appropriate reactants. Yields approximately quantitative in all cases.

p-Tolyl sulphone of (I)	M. p. and mixed m. p. 160°.
p-Tolyl sulphone of (II)	M. p. 120° from ethyl alcohol (Found: S, 11·7. Calc. for $C_{15}H_{16}O_3S$: S, 11·6%).
p-Tolyl thioether of (I)	M. p. 87—88° from ethyl alcohol. Gives the sulphone (m. p. and mixed m. p. 160°) on oxidation with hydrogen peroxide–glacial acetic acid.
p-*Tolyl thioether* of (II)	M. p. 66—67° from methyl alcohol (Found: S, 12·9. $C_{15}H_{16}OS$ requires S, 13·1%).
p-*Tolyl thioether* of (IV)	M. p. 58° from methyl alcohol (Found: S, 12·6. $C_{16}H_{18}OS$ requires S, 12·4%).
Phenyl ether of (I) [*dl*- from (+)phthalate]	M. p. 83—84° from methyl alcohol (Found: C, 82·4; H, 6·0; OMe, 9·9. $C_{20}H_{18}O_2$ requires C, 82·7; H, 6·2; OMe, 10·7%).
Phenyl ether of (V)	M. p. 104° from ethyl alcohol (Found: C, 85·0; H 6·0; *M* (Rast), 334. $C_{24}H_{20}O_2$ requires C, 84·7; H, 5·9%; *M*, 340).
1-*Naphthyl ether* of (I)	M. p. 122—123° from ethyl alcohol (Found: C, 85·2; H, 6·1; *M* (Rast), 360. $C_{24}H_{20}O_2$ requires C, 84·7; H, 5·9%; *M*, 340).

Reactions with Aqueous Ammonia and Methylamine.—From a solution of *dl*-*p*-methoxybenzhydryl hydrogen phthalate (9 g.) in concentrated aqueous ammonia (90 c.c.) at room temperature an oil separated, which was combined with ether washings from the supernatant liquid, washed with alkali and with water, dried, and concentrated. From the resulting impure *p*-methoxybenzhydrylamine (1 g.), warmed with acetic anhydride for a few minutes and poured into water, the acetyl derivative, silky needles, m. p. 159—160° from ethyl alcohol, was obtained (Hantzsch and Kraft, *Ber.*, 1891, **24**, 3513, give m. p. 159°). The impure amine (0·8 g.), with sodium hydroxide (4 c.c. of 2·5N) and benzoyl chloride (0·6 g.), gave the benzoyl derivative, m. p. 180—181° from ethyl alcohol (Busch and Leefhelm, *J. pr. Chem.*, 1908, **77**, 20, give m. p. 174°) (Found: C, 79·7; H, 6·2; N, 4·0. Calc. for $C_{16}H_{17}O_2N$: C, 79·5; H, 6·0; N, 4·4%).

From 3 g. of the same phthalate in 20 c.c. of aqueous methylamine solution (33% w/v), *p*-methoxybenzhydrol (1·6 g.) separated after 48 hours at room temperature, m. p. and mixed m. p. 64—65°.

From *dl*-*p*-phenoxybenzhydryl hydrogen phthalate (3 g.) in aqueous ammonia (20 c.c.) after 30 minutes at 100° (sealed tube), impure *p*-phenoxybenzhydrylamine (1·4 g.) separated, yielding with acetic anhydride the *acetyl* derivative, needles from methyl alcohol, m. p. 166° (Found: N, 4·7. $C_{21}H_{19}O_2N$ requires N, 4·5%). Similarly, from the hydrogen phthalate of anisyl-1-naphthylcarbinol (3 g.) in concentrated aqueous ammonia (20 c.c.) at 100° and acetylation of the crude amine, the *acetyl* derivative of anisyl-1-naphthylmethylamine was obtained, m. p. 197° from ethyl alcohol (Found: C, 79·0; H, 6·0; N, 4·5. $C_{21}H_{19}O_2N$ requires C, 78·7; H, 6·2; N, 4·6%).

From a solution of benzhydryl phthalate (2 g.) in aqueous ammonia (15 c.c.) after 7 days at room temperature, benzhydrol (0·2 g.; m. p. and mixed m. p. 68°) separated, but most of the phthalate was recovered unchanged. From a solution of anisyl hydrogen phthalate (9 g.) in aqueous ammonia (20 c.c.) after 2 hours at 100° (sealed tube), anisyl alcohol (m. p. and mixed m. p. 22°) was obtained quantitatively.

Reactions of p-*Methoxybenzhydryl Hydrogen Phthalate with Oxime and* aci-*Nitro Salts.*—(viii) (+)Phthalate (7·2 g.) was dissolved in a solution of *o*-methoxy-α-benzaldoxime (4·5 g.; m. p. 92°) in 150 c.c. of 0·3N-sodium hydroxide. An oil separated from the filtered solution after 12 hours; it was solidified by trituration with light petroleum and recrystal-

lised from ethyl alcohol, yielding the O-p-*methoxybenzhydryl ether* of *o*-methoxybenzaldoxime (4·2 g.), m. p. 81° (Found: C, 75·9; H, 6·4; N, 4·1. $C_{22}H_{21}O_3N$ requires C, 76·1; H, 6·1; N, 4·0%). This ether (1 g.) was dissolved in glacial acetic acid (25 c.c.) and reduced with zinc dust (2 g., activated by shaking with acidified 3% copper sulphate solution). The zinc dissolved at room temperature, and the solution was filtered, made alkaline, and extracted with ether. The oil isolated from the ether was dissolved in ethyl acetate; on addition of hydrochloric acid, *o*-methoxybenzylamine hydrochloride separated, shining plates from ethyl alcohol–ether, m. p. 150° (Goldschmidt and Ernst, *Ber.*, 1890, **23**, 2742, give m. p. 150°) (Found: N, 8·2; Cl, 20·5. Calc. for $C_8H_{11}ON,HCl$: N, 8·1; Cl, 20·4%). (ix) Phthalate (3·6 g.) was added to a solution of *p*-nitro-α-benzaldoxime (3·3 g.), m. p. 129° (Gabriel and Herzbert, *Ber.*, 1883, **16**, 2000), in sufficient 0·3N-sodium hydroxide for complete solution. The oil, (2·9 g.) which separated (24 hours) hardened on trituration with ligroin. The O-p-*methoxybenzhydryl ether* of *p*-nitro-α-benzaldoxime, small yellow prisms from ethyl alcohol or ligroin, had m. p. 115—116° (Found: N, 7·8. $C_{21}H_{18}O_3N_4$ requires N, 7·7%).

(x) Phthalate (3·6 g.) and cupferron (3 g.) were dissolved in sodium hydroxide solution (38 c.c.; 0·3N). The oil which separated (18 hours) crystallised from hot ethyl alcohol. Repeated crystallisation (alcohol or benzene) and decolorisation (charcoal) gave the p-*methoxybenzhydryl ether* of *N*-nitrosophenylhydroxylamine, m. p. 114° (decomp.) (Found: N, 8·1. $C_{20}H_{18}O_3N_2$ requires N, 8·4%).

(xi) *p*-Bromobenzyl bromide (Schramm, *Ber.*, 1884, **17**, 2922) was converted into the cyanide (Jackson and Lowery, *J. Amer. Chem. Soc.*, 1881, **3**, 242) and this into the sodium salt of *p*-bromophenyl*iso*nitromethane (Wislicenus and Elvert, *Ber.*, 1908, **41**, 4121). From a solution of this sodium salt (3·0 g.) and the phthalate (3·6 g.) in 0·3N-sodium hydroxide (40 c.c.) a sticky solid separated, which was dissolved in ether, washed with alkali, and dried. The needles which crystallised from the ether (1·4 g.; m. p. 170—190°) crystallised from most organic solvents, giving the p-*methoxybenzhydryl ether* (*nitronic ester*) of *p*-bromophenylnitromethane, m. p. 192° [Found: C, 61·4; H, 4·4; N, 3·2; Br, 18·9; *M* (Rast), 448. $C_{21}H_{18}O_3NBr$ requires C, 61·2; H, 4·4; N, 3·4; Br, 18·9%; *M*, 412]. This substance was insoluble in hot alkali, gave no coloration with ferric chloride, and did not liberate iodine from hydriodic acid or absorb bromine from alcoholic solution. The solution decanted from the crude ether yielded *p*-methoxybenzhydrol (1 g.) and a little of its neutral phthalic ester. (xii) From the phthalate and the sodium salts of phenylnitromethyl cyanide, phenylnitromethane, and nitromethane, by methods as in (x) above, oils separated, which after being washed with alkali, contained nitrogen (*i.e.*, were probably crude nitronic esters) but could not be crystallised or distilled.

From the hydrogen phthalate (2·1 g.) of *o*-methoxyphenyl-1-naphthylcarbinol (Part III) the O-*ether* of *o*-methoxybenzaldoxime (1·8 g.) was obtained as in (viii) after 1 week at room temperature; m. p. 144—145° from methylene chloride (Found: N, 3·6. $C_{18}H_{23}O_3N$ requires N, 3·5%).

Reactions of Carbinols.—These were done with carbinols (I)—(V) listed above, and 3 : 4-dimethoxybenzhydrol (VI), anisylxenyl carbinol (VII), *p*-dimethylaminobenzhydrol (Part III) (VIII), and triphenylcarbinol (IX). (VI), m. p. 99°, was obtained by reduction (zinc dust in alcoholic sodium hydroxide) of the ketone (Friedel–Crafts reaction on veratrole; Sachs and Thonet, *Ber.*, 1904, **37**, 3332; Brüggeman, *J. pr. Chem.*, 1896, **53**, 253). *Anisylxenylcarbinol* (VII), m. p. 108—109° from benzene–ligroin (Found: C, 82·5; H, 6·3. $C_{20}H_{18}O_2$ requires C, 82·8; H, 6·2%), was obtained by similar reduction of *anisyl xenyl ketone*, m. p. 157—158° from ligroin (Found: C, 83·1; H, 5·6. $C_{20}H_{16}O_2$ requires C, 83·3; H, 5·6%), the ketone having been obtained by Friedel–Crafts reaction from anisoyl chloride and diphenyl. The reactions (products listed below) were conducted by heating the carbinols under reflux in chloroform with approximately equal weights of *p*-toluenesulphinic acid or thio-*p*-cresol, respectively for 4—18 hours. Yields approximately quantitative.

p-Tolyl sulphone of (I)	M. p. and mixed m. p. 87—88°.
p-Tolyl sulphone of (III)	M. p. and mixed m. p. 164°; *dl*-sulphone from (+)carbinol.
p-*Tolyl sulphone* of (VI)	M. p. 146—147° from ethyl alcohol (Found: S, 8·4. $C_{22}H_{22}O_4S$ requires S, 8·4%).
p-*Tolyl sulphone* of (VII)	M. p. 165° from ethyl alcohol (Found: S, 7·7. $C_{27}H_{26}O_3S$ requires S, 7·5%).
p-Tolyl thioether of (I)	M. p. and mixed m.p. 87—88°.
p-*Tolyl thioether* of (III)	M. p. 55—56° from methyl alcohol (Found: S, 8·2. $C_{26}H_{22}OS$ requires S, 8·3%).
p-*Tolyl thioether* of (IV)	M. p. 58° from methyl alcohol (Found: S, 12·6. $C_{16}H_{16}O_3$ requires S, 12·6%).
p-*Tolyl thioether* of (VI)	M. p. 74—75° from methyl alcohol (Found S, 8·7. $C_{23}H_{22}O_2$ requires S, 9·2%).
p-*Tolyl thioether* of (VIII)	M. p. 91° from methyl alcohol (Found: S, 9·8. $C_{23}H_{23}NS$ requires S, 9·6%).
p-*Tolyl thioether* of (IX)	M. p. 149° from methyl alcohol (Found: S, 8·7. $C_{26}H_{22}S$ requires S, 8·7%).

Anisyl hydrogen phthalate (10 g.), heated under reflux in 30 c.c. of ethyl alcohol, yielded the ethyl ether (2·7 g.), b. p. 115°/13 mm., 116—117°/14 mm., $n_D^{21°}$ 1·5060 (Späth, *Monatsh.*, 1914, **35**, 330, gives b. p. 111—113°/11 mm.). From a solution of the same phthalate (20 g.) after heating under reflux in chloroform (40 c.c.) for 45 hours phthalic acid separated; unchanged hydrogen phthalate was removed from the chloroform by washing with dilute aqueous sodium hydroxide, and evaporation of the chloroform then yielded anisyl phthalate (6·2 g.), an undistillable oil which on hydrolysis yielded anisyl alcohol (m. p. and mixed m. p. 22°) and phthalic acid.

Di-p-*methoxybenzhydryl ether* (Part II, *loc. cit.*). The hydrol (2·1 g.) with *p*-toluenesulphonic acid (5·2 g.) in water (20 c.c.) was warmed on the steam-bath for 20 minutes. The resulting oil crystallised (1·9 g.) from ligroin in glassy plates and after one recrystallisation from ethyl alcohol had m. p. and mixed m. p. 120—121°.

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BATTERSEA POLYTECHNIC, LONDON, S.W.11. [*Received, February 28th*, 1946.]

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171. *Syntheses of 9-Substituted Flavins as Antimalarials.*

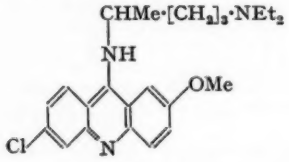
By MOSHÉ M. NEEMAN.

Mepacrine (atebrin) antagonizes the prosthetic group of cytochrome reductase, *viz.*, riboflavin phosphate. With a view of enhancing the action of the drug, compounds (II) and (III) have been synthesized in which the *iso*alloxazine nucleus has been substituted for the acridine nucleus in mepacrine, with retention of the known pharmacodynamic groups of this drug.

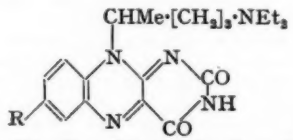
THE antimalarial activity of mepacrine depends on inhibition of the respiration of the parasite (Christophers, *Trans. Faraday Soc.*, 1943, **265**, 333), and seems mainly due to the irreversible combination of the drug with the protein moiety of cytochrome reductase (Haas, *J. Biol. Chem.*, 1944, **155**, 321). Addition of the prosthetic

group to the enzyme before addition of the drug, however, antagonized the action of mepacrine successfully by suppression of the dissociation of the enzyme. One molecule of riboflavin phosphate " neutralised " about 500 molecules of mepacrine. It appears, therefore, that mepacrine is still rather remote from the structure of the " ideal antagonist " of riboflavin (IV).

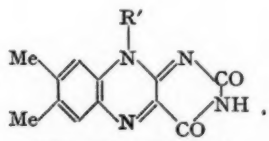
We considered it promising to change the structure of mepacrine (I) by substitution of the *iso*alloxazine for the acridine nucleus, with retention of those parts of mepacrine known for their pharmacodynamic properties.



(I.)



(II; R = H.) (III; R = Cl.)



(IV; R' = Ribityl.)

While lack of halogen in mepacrine appears dystherapeutic (cf. Williams, "Chemotherapy of Malaria," Lederle Lab. Inc., 1941, p. 218), both condensed benzene rings of the acridine nucleus are by no means indispensable for antimalarial activity (Gilman and Spatz, *J. Amer. Chem. Soc.*, 1944, **66**, 622; Galperin, *Med. Parasit. and Parasit. Dis.*, 1940, **9**, 44; Magidson and Rubtsov, *J. Gen. Chem. Russia*, 1937, **7**, 1896). Although it is impossible to predict *a priori* the biological activity of a new compound, the flavins (II) and (III) seemed a promising approach.

As far as we are aware only one flavin with a basic side chain is known, which has been prepared by Karrer and Naef (*Helv. Chim. Acta*, 1936, **19**, 1029), by condensation of an *N*-(ω-phthalimidoalkyl)phenylenediamine with alloxan. Our flavins were synthesized by condensation of *N*-(ω-diethylaminoalkyl)phenylenediamines with alloxan by the method of Kuhn and Weygand (*Ber.*, 1935, **68**, 1282).

The purification of the flavins was laborious as they could not be induced to crystallize, and numerous attempts to prepare complex salts and derivatives failed to give well-defined products. The isolation of these flavins succeeded only after finding that they gave slightly soluble Reineckates which were easily obtained in the pure state.

While biological tests on the substances described were under progress, a paper describing unsuccessful attempts to prepare flavins substituted at 9 with dialkylaminoalkyl groups came to our attention (Hall and Turner, *J.*, 1945, 699).

Results of biological tests will be published elsewhere.

Experimental.

2-Amino-5-diethylaminopentane was prepared by catalytic reduction of methyl 3-diethylaminopropyl ketone in alcoholic ammonia in presence of Raney nickel. The aminoketone (92 g., 0·59 mol.) was dissolved in 15% alcoholic ammonia (1200 c.c.). Raney nickel (30 g.) was added and the reduction carried out at 40° and at atmospheric pressure. When absorption of hydrogen was complete, the catalyst was filtered off. The alcohol was removed and the product distilled in a vacuum, b. p. 92°/30 mm. Yield, 75 g. (82%).

o-Nitro-N-(*δ-diethylamino-α-methylbutyl*)*aniline*.—A solution of *o*-dinitrobenzene (25 g., 0·15 mol.) and 2-amino-5-diethylaminopentane (26 g., 0·16 mol.) in *p*-cymene (400 c.c.) was heated under reflux for 3 hours. After cooling the product was extracted with dilute hydrochloric acid. The acidic liquid was extracted with ether to remove non-basic substances. After cooling strongly excess of 50% aqueous sodium hydroxide was added and the product was extracted by ether. The solvent was removed and the *product* was distilled in a vacuum, b. p. 165°/0·8 mm. A dark red viscous oil was obtained, $n_D^{27°}$ 1·5725. Yield, 25 g. (60%) (Found: C, 64·0; H, 9·3. $C_{15}H_{25}O_2N_3$ requires C, 64·3; H, 9·0%).

N-(*δ-Diethylamino-α-methylbutyl*)-*o-phenylenediamine*.—*o*-Nitro-*N*-(δ-diethylamino-α-methylbutyl)aniline (20 g., 0·07 mol.) was dissolved in alcohol (150 c.c.). Palladium catalyst (2% Pd on calcium carbonate, 0·5 g.) was added. The nitro-compound was reduced with slow addition of hydrogen at atmospheric pressure, as the reaction was exothermic. When absorption of hydrogen was complete the catalyst was filtered off, the alcohol was removed, and the product was distilled in a vacuum. The crude product darkened easily, but the pure *product* was quite stable. A colourless oil was obtained, b. p. 144°/0·2 mm., $n_D^{27°}$ 1·5349. Yield, 16 g. (90%) (Found: C, 71·8; H, 11·1. $C_{15}H_{27}N_3$ requires C, 72·3; H, 10·8%).

9-(*δ-Diethylamino-α-methylbutyl*)iso*alloxazine* (II).—*N*-(δ-Diethylamino-α-methylbutyl)-*o*-phenylenediamine (10 g., 0·04 mol.) was dissolved in glacial acetic acid (20 c.c.). Alloxan monohydrate (6·4 g., 0·04 mol.) and boric acid (3 g., 0·05 mol.) in glacial acetic acid (60 c.c.) were heated to boiling, and then cooled to 40°. The solution of the diamine was then added to the solution of the boric acid. A strong green fluorescence immediately appeared. The reaction mixture was kept for two days at 37°. The acetic acid was then distilled off under reduced pressure, and the residue was taken up in water. The solution was steam distilled. The residue was concentrated under reduced pressure to 35 c.c. A part of this solution was neutralised with hydrochloric acid and the flavin was precipitated with a concentrated aqueous solution of Reinecke salt. The yellow precipitate was filtered off and washed with a small amount of water. The *compound* was soluble in acetone. It darkened at 120° and decomposed at about 190°. It was dried in a vacuum over phosphorus pentoxide at 40° to constant weight (Found: C, 38·9; H, 5·2; Cr_2O_3, 11·3. $C_{19}H_{25}O_2N_5[Cr(NH_3)_2(CNS)_4]H,2H_2O$ requires C, 38·9; H, 5·1; Cr_2O_3, 10·7%). Another part of the original solution of the flavin was evaporated to dryness under reduced pressure and extracted with absolute ethanol. The ethanol was removed under reduced pressure and the flavin was taken up in water giving a solution which showed strong green fluorescence. The flavin was adsorbed on frankonite (active charcoal was also effective, while fuller's earth gave poor adsorption). The flavin was eluted with acetic acid–pyridine. Adsorption was very strong and large amounts of eluent were required. The eluent was removed under reduced pressure, and the flavin was taken up in water and precipitated as the Reineckate by the method given above. The same product as from the original solution of the flavin was obtained.

4-Chloro-2-nitro-N-(*δ-diethylamino-α-methylbutyl*)*aniline*.—2 : 5-Dichloronitrobenzene (19 g., 0·1 mol.) was refluxed

with 2-amino-5-diethylaminopentane (80 g., 0·5 mol.) for 16 hours. Excess of diamine was distilled off under reduced pressure. The residue was taken up in dilute hydrochloric acid. The acidic liquid was extracted with ether. The aqueous layer was cooled, and excess of 50% aqueous sodium hydroxide was added to it. The product was extracted with ether. The solvent was removed and the product was fractionated in a vacuum to give a viscous red *oil*, b. p. 187°/0·5 mm., 177°/0·02 mm., $n_D^{22°}$ 1·5750. Yield, 28 g. (93%) (Found: C, 58·2; H, 7·8. $C_{15}H_{24}O_2N_3Cl$ requires C, 57·4; H, 7·7%).

Attempted catalytic reduction of the above nitro-compound in presence of palladium on calcium carbonate gave a chlorine-free oil which was shown by analysis to be the de-halogenated product N-(δ-*diethylamino-α-methylbutyl*)-o-*phenylenediamine* (Found: C, 73·0; H, 10·7. $C_{15}H_{27}N_3$ requires C, 72·3; H, 10·8%).

4-*Chloro*-N-(δ-*diethylamino-α-methylbutyl*)-1 : 2-*phenylenediamine*.—4-Chloro-2-nitro-*N*-(δ-diethylamino-α-methylbutyl)aniline (14 g., 0·045 mol.) was dissolved in concentrated hydrochloric acid (25 c.c.) at 5°. Tin foil (23 g.) was dissolved in concentrated hydrochloric acid (125 c.c.). This solution was filtered and warmed to 40°. To this the solution of the nitroaniline was added in small portions with stirring. The reaction mixture quickly turned pale yellow. It was heated to 50° for 2 hours. After cooling it was poured into 30% aqueous sodium hydroxide (150 c.c.), the temperature being kept below 30°. A yellow viscous oil floated on top of the alkaline liquid. The product was extracted by ether, the solvent was removed, and the *product* distilled in a vacuum, b. p. 160°/0·05 mm., $n_D^{28°}$ 1·5450. Yield, 11 g. (88%) (Found: C, 64·2; H, 9·3. $C_{15}H_{26}N_3Cl$ requires C, 63·5; H, 9·2%).

6-*Chloro*-9-(δ-*diethylamino-α-methylbutyl*)*isoalloxazine* (III).—This flavin was prepared by the same method as (II). 4-Chloro-*N*-(δ-diethylamino-α-methylbutyl)-1 : 2-phenylenediamine (21·5 g., 0·076 mol.), alloxan monohydrate (12·15 g., 0·076 mol.), boric acid (4·7 g., 0·76 mol.), and glacial acetic acid (115 c.c.) were used. The reaction mixture was worked up as before and a brownish *Reineckate* was obtained. It decomposed slowly between 150° and 200°, the temperature of decomposition depending on the rate of heating (Found: C, 36·7; H, 4·4; Cr_2O_3, 10·9. $C_{19}H_{24}O_3N_5Cl[Cr(NH_3)_2(CNS)_4]H,2H_2O$ requires C, 37·1; H, 4·7; Cr_2O_3, 10·2%).

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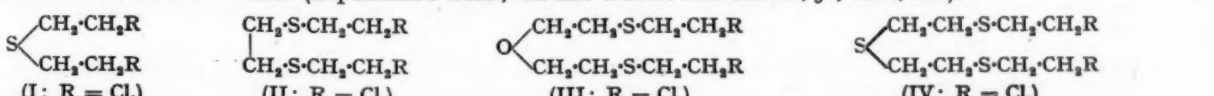
172. *The Methyl Thioethers derived from 2 : 2′-Dichlorodiethyl Sulphide and its Analogues. Part I. Possible Uses for Analysis.*

By E. M. MEADE and (the late) R. C. G. MOGGRIDGE.

2 : 2′-Dichlorodiethyl sulphide (" mustard gas ") (I) and its higher analogues (II—IV) react with sodium thiomethoxide to give the corresponding methyl thioethers (V—VIII). These are low-melting solids and can be separated by distillation. Attempts have been made to use them for analysis of mixtures of mustard gas and its higher analogues, for which no other method of separation is available. Only partial success has been achieved, since it has been found that small amounts of the thioethers (VI) and (VIII) can be isolated after treatment of pure mustard gas with the thiomethoxide.

THE study of mixtures of 2 : 2′-dichlorodiethyl sulphide (" mustard gas ") (I) with its higher analogues, *e.g.*, 1 : 2-di-(2-chloroethylthio)ethane (II), 2 : 2′-di-(2-chloroethylthio)diethyl ether (III), or 2 : 2′-di-(2-chloroethylthio)diethyl sulphide (IV), is complicated by the difficulty of separating the constituents; it is hard to obtain even approximate estimates of the amounts of the various compounds present. Their chemical similarity makes it hard to devise any chemical differentiation; and, while mustard gas can be distilled at reduced pressures without decomposition, the other three compounds decompose on attempted distillation at pressures of the order of 1—5 mm. (unpublished work; cf. also Davies and Oxford, *J.*, 1931, 224).



(I; R = Cl.) (V; R = SMe.) (II; R = Cl.) (VI; R = SMe.) (III; R = Cl.) (VII; R = SMe.) (IV; R = Cl.) (VIII; R = SMe.)

This paper describes an attempt to overcome these difficulties by preliminary conversion into the *methyl thioethers* (V—VIII). These are readily obtained in very high yield by the action of alcoholic sodium thiomethoxide on the chloro-compounds. They crystallise readily and can be distilled without apparent decomposition; their stability and non-vesicant nature make them much easier to handle than the parent chloro-compounds. The corresponding *sulphones* are obtained by action of peracetic acid.

The methyl thioethers appeared to be suitable for distillation analysis, and reasonable results were obtained in control experiments with synthetic mixtures of (I), (II), and (IV). It was therefore hoped that the method would prove useful for approximate analyses of mustard gas mixtures. In the course of such analytical experiments, however, two observations were made which suggested that the application of the method to problems requiring any delicacy of analysis was unsound. Thus:

(*a*) During analyses, particularly in cases when, owing to the presence of tarry residues, the mixtures had to be heated strongly to ensure complete distillation, low-boiling products were observed. These presumably indicated the presence of decomposition reactions, and therefore cast doubt on the quantitative nature of the analysis. An investigation into the nature of the products of decomposition of (V) is described in Part II of this series (Charnock and Moggridge, following paper).

(*b*) When the formation of the methyl thioether from mustard gas was studied carefully, it was found that the product contained small amounts of (VI) and (VIII); the amounts isolated from pure mustard gas were of the order of 1% and 0·02% (molar ratios) respectively. Pure (V) could be repeatedly redistilled without any sign of (VI) or (VIII) being observed; it therefore appears that these compounds were produced

not during the distillation but during the reaction with the thiomethoxide. The occurrence of this reaction was so unexpected as to cast some doubt on the structure of the compounds concerned; these have, however, since been confirmed by independent syntheses (cf. Part III, Brown and Moggridge, this vol., p. 816). It seems possible that the mechanism of this reaction may be similar to that proposed by Bell, Bennett, and Hock (*J.*, 1927, 1803) for the analogous formation of 1 : 2-di-(2-cyanoethylthio)ethane when mustard gas is treated with potassium cyanide (Davies, *J.*, 1920, **117**, 297).

The occurrence of this reaction, even though only to a small extent, clearly attacks the logical basis of the analytical method. It is concluded that the results given by the method can at best only be regarded as rough approximations; in particular, that the isolation of small amounts of (VI) and (VIII) must not be taken as evidence of the presence of (II) and (IV) in the original mixture.

Experimental.

Starting materials were mustard gas (I) (cf. Clarke, *J.*, 1912, **101**, 1583); 1 : 2-di-(2-chloroethylthio)ethane (II) (cf. Bennett and Whincop, *J.*, 1921, 1862); 2 : 2′-di-(2-chloroethylthio)diethyl ether (III) (cf. Davies and Oxford, *loc. cit.*; Woodward, private communication); and 2 : 2′-di-(2-chloroethylthio)diethyl sulphide (IV) (Woodward, private communication).

Preparation of the Thioethers.—To the chloro-compound (1 equiv.) in a large flask fitted with an efficient reflux was added a solution of sodium thiomethoxide in alcohol, prepared by distilling methylthiol (1·3 equivs.; *Org. Synth.*, Coll. Vol. **2**, 346) into sodium ethoxide solution (from 1·25 equivs. of sodium). The mixture was cautiously warmed, and the vigorous reaction which ensued was completed by refluxing for 30 minutes. Then, either (*a*) the mixture was cooled, sodium chloride removed by filtration, and the filtrate evaporated to dryness under reduced pressure, or (*b*) equal volumes of chloroform and dilute acid were added to the mixture, and the chloroform layer was separated. The aqueous layer was again extracted with chloroform, and the combined extracts were dried and evaporated to dryness under reduced pressure. In either case the crude thioether was obtained in almost theoretical yield and was purified by distillation; yield of distilled material 80—90%.

For conversion into the sulphone the thioether was treated with a large excess (in a typical case 20 c.c. for 0·25 g. of thioether) of a mixture (1 : 1) of perhydrol and glacial acetic acid. A reaction occurred with evolution of heat; it was completed either by keeping at room temperature for 24—48 hours, or by heating at 100° for 1 hour. The crude sulphone was in either case deposited from the reaction mixture in 80—90% yield.

2 : 2′-*Dimethylthiodiethyl sulphide* (V) had m. p. 24·3°, b. p. 118°/1 mm., 125°/2·5 mm., 137°/6 mm., about 260°/760 mm.; $d^{25°}$ 1·08935 (temperature gradient, 0·00085 per degree); $n^{25°}$ 1·55835 (temperature gradient, 0·00045 per degree); [*R*] 53·89 (calc., 53·83) (Found: S, 52·4. $C_6H_{14}S_3$ requires S, 52·7%). 2 : 2′-*Dimethylsulphonyldiethyl sulphone* formed colourless plates from aqueous acetic acid (50%), m. p. (no decomp.) 265° (Found: C, 25·5; H, 4·95; S, 35·16. $C_6H_{14}O_6S_3$ requires C, 25·85; H, 5·08; S, 34·5%).

1 : 2-*Di*-(2-*methylthioethylthio*)*ethane* (VI) formed colourless plates from alcohol or light petroleum, m. p. 66·5°, b. p. 180—185/6 mm. (Found: S, 52·95. $C_6H_{18}S_4$ requires S, 52·9%). 1 : 2-*Di*-(2-*methylsulphonylethylsulphonyl*)*ethane* formed colourless needles from aqueous acetic acid (50%), m. p. 210° (Found: S, 34·8. $C_6H_{18}O_8S_4$ requires S, 34·6%).

2 : 2′-*Di*-(2-*methylthioethylthio*)*diethyl ether* (VII) formed colourless plates from light petroleum, m. p. 37°, b. p. 210°/1 mm. (Found: S, 44·35. $C_{10}H_{22}OS_4$ requires S, 44·7%). 2 : 2′-*Di*-(2-*methylsulphonylethylsulphonyl*)*diethyl ether* formed colourless plates from aqueous acetic acid (50%), m. p. 198° (Found: S, 31·1. $C_{10}H_{22}O_9S_4$ requires S, 30·95%).

2 : 2′-*Di*-(2-*methylthioethylthio*)*diethyl sulphide* (VIII) formed colourless needles from alcohol or light petroleum, m. p. 88° (Found: S, 53·2. $C_{10}H_{22}S_5$ requires S, 53·0%). 2 : 2′-*Di*-(2-*methylsulphonylethylsulphonyl*)*diethyl sulphone* was insoluble in all normal solvents, but was crystallised from a mixture of water and concentrated nitric acid (equal vols.); colourless needles, m. p. 220° (decomp.) (Found: S, 34·4. $C_{10}H_{22}O_{10}S_5$ requires S, 34·6%).

Control Analytical Experiments.—The following is typical of several control experiments. The synthetic dichloro-compounds (I), (II), and (IV) were mixed in a weight ratio of 10, 75, and 15% respectively. 19·7 G. of this mixture were converted into the thioethers, which were separated by distillation; weights of fractions 2·7, 14·8, and 2·65 g. respectively, giving ratio of chloro-compounds found 13, 73·5, and 13·5% respectively.

Isolation of (VI) *and* (VIII) *from the Products of Interaction of Mustard Gas and Sodium Thiomethoxide.*—In these experiments the reaction with the thiomethoxide solution was carried out as usual and the crude product twice distilled. The residues from these distillations were mixed and distilled in small solid-distillation flasks until the (VI) fraction was obtained solid at room temperature. Final purification was then effected by recrystallisation. The residues from the solid distillations were recrystallised to give (VIII).

The results of these experiments are given below. The m. p. of pure mustard gas is generally given as 14·35°. The quoted yields refer to material melting at 63° for (VI), and 84° for (VIII). The purification necessary refers to (VI). Both compounds were identified by mixed m. p. with synthetic specimens.

(1) 76 G. of mustard gas, m. p. 13·8°. Residue split by distillation into three fractions; purification necessary ranged from 2 distillations and 1 recrystallisation to 4 distillations and 2 recrystallisations. Total yields—(VI), 1·9 g.; (VIII), 0·02 g.

(2) 133 G. of mustard gas, m. p. 14·1°. Purification necessary, 2 distillations, 3 recrystallisations. Yield of (VI), 1·4 g.; of (VIII), 0·04 g.

(3) 100 G. of mustard gas, m. p. 14·35°. Purification necessary, 1 distillation, 3 recrystallisations. Yield of (VI), 1·4 g.; of (VIII), 0·04 g.

Control Experiments.—(*a*) Pure (V) was repeatedly redistilled under conditions identical with those used in the above experiments. The distillation residues were very small and no sign of (VI) or (VIII) could be detected by their distillation or recrystallisation.

(*b*) Pure (VI) was added to batches of 17—20 g. of pure (V), and isolation experiments carried out exactly as above. The results were as follows:

(i) 3·0 G. of (VI) added. Purification necessary, one distillation. Recovery, 87%.
(ii) 1·5 G. of (VI) added. Purification necessary, one distillation. Recovery, 73%.
(iii) 1·0 G. of (VI) added. Purification, 1 distillation and 2 recrystallisations. Recovery, 50%.

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Research Establishment, Sutton Oak. [*Received, January 23rd*, 1946.]

173. *The Methyl Thioethers derived from 2 : 2′-Dichlorodiethyl Sulphide and its Analogues. Part II. Pyrolysis Experiments.*

By R. J. Charnock and (the late) R. C. G. Moggridge.

The following compounds have been isolated from the products of pyrolysis of 2 : 2′-dimethylthiodiethyl sulphide (I) : methylthiol (II), methyl vinyl sulphide (IV), 2-methylthioethylthiol (V), dithian, and the compound (VI). (VI) is thought to arise by the spontaneous combination of 2-methylthioethyl vinyl sulphide (III) and (V). 1 : 2-Dimethylthioethane (VII) was also isolated as a secondary reaction product, probably formed by the combination of (II) and (IV).

These results confirm the conclusion from Part I that the isolation of small amounts of (VI) from the products of reaction of sodium thiomethoxide on mustard gas mixtures must not be taken as proof that these mixtures contain 1 : 2-di-(2-chloroethylthio)ethane (VIII).

In Part I of this series (Meade and Moggridge, preceding paper) the presence of low-boiling material obtained on distillation of this family of thioethers was noted. It seemed likely that this material resulted from decomposition; and, in view of the possible use of these compounds for distillation analysis, it was decided that the nature of this decomposition ought to be studied in greater detail.

2 : 2′-Dimethylthiodiethyl sulphide (I; cf. Part I) was therefore subjected to pyrolysis, being heated to boiling at atmospheric pressure for 2½ hours. The following compounds were isolated from the complex mixture of products: methylthiol (II), *methyl vinyl sulphide* (IV), 2-methylthioethylthiol (V), dithian, unchanged (I), and, in low yield, 1 : 2-di-(2-methylthioethylthio)ethane (VI). The structure of (IV) was confirmed by reaction with phenylthiol to give 1-*phenylthio*-2-*methylthioethane*, and oxidation of this to the corresponding *disulphone*.

Rothstein (*J.*, 1940, 1550 *et seq.*) has predicted on theoretical grounds that a compound of the type CHAR·CH_2·SR′ (where A is a group capable of forming a stable anion) will be liable to decompose to give R·CH=CH·SR′ + HA. If this is applied to the compound (I) the following decomposition routes would be expected :

$$\underset{\text{(I.)}}{\text{MeS·CH}_2\text{·CH}_2\text{·S·CH}_2\text{·CH}_2\text{·SMe}} \begin{cases} \rightarrow \text{MeSH} + \underset{\text{(III.)}}{\text{MeS·CH}_2\text{·CH}_2\text{·S·CH:CH}_2} & \text{(II.)} \\ \rightarrow \underset{\text{(IV.)}}{\text{MeS·CH:CH}_2} + \underset{\text{(V.)}}{\text{MeS·CH}_2\text{·CH}_2\text{·SH}} \end{cases}$$

It is seen that these routes provide a ready explanation for the formation of (II), (IV), and (V). The fact that (III) was not isolated should not, it is considered, be taken as evidence against the decomposition routes; the complexity of the mixture obtained after pyrolysis made the isolation of the constituents difficult, and it is not at all improbable that (III) was present though never isolated. The presence of dithian shows that some more complex decomposition mechanisms were also involved. The formation of (VI) is discussed below.

$$\underset{\text{(VI.)}}{\begin{matrix}\text{CH}_2\text{·S·CH}_2\text{·CH}_2\text{·SMe} \\ \text{CH}_2\text{·S·CH}_2\text{·CH}_2\text{·SMe}\end{matrix}} \qquad \underset{\text{(VII.)}}{\text{MeS·CH}_2\text{·CH}_2\text{·SMe}} \qquad \underset{\text{(VIII.)}}{\begin{matrix}\text{CH}_2\text{·S·CH}_2\text{·CH}_2\text{Cl} \\ \text{CH}_2\text{·S·CH}_2\text{·CH}_2\text{Cl}\end{matrix}}$$

1 : 2-Dimethylthioethane (VII) was also isolated from the pyrolysis experiments as a result of a curious secondary reaction. Methyl vinyl sulphide (IV) was first obtained from the pyrolysis mixture as a crude fraction, b. p. 40—80°, at atmospheric pressure. When this fraction was redistilled immediately the compound (IV) was obtained pure, and no sign of high-boiling material was noted. When, however, the crude fraction was kept for some hours before it was redistilled, it was found to contain appreciable quantities of higher-boiling (60°/5 mm.) compound (VII), identified by oxidation to its disulphone (cf. Otto, *J. pr. Chem.*, 1887, **36**, 445).

It is thought that the explanation of this phenomenon is that the crude material, b. p. 40—80°, contained appreciable quantities of dissolved methylthiol; and that this compound, if not immediately removed by distillation, reacted with (IV) to give (VII).

The suspected occurrence of this reaction suggested that the other thiols and vinyl compounds present in the pyrolysis mixture might also combine spontaneously. Thus (II) and (III), (IV) and (V) could recombine to give (I); while (III) and (V) would give (VI). The spontaneous occurrence of several of these thiol–vinyl additions [of (II) to (IV), (IV) to (V), and (III) to (V)] has since been demonstrated (cf. Part III, following paper). The occurrence of (VI) among the breakdown products of (I), which at first sight appears puzzling owing to the relative sizes of the two molecules, can thus be plausibly explained as a result of the recombination of (III) and (V).

The occurrence of (VI) is of significance in that its isolation after treating mixtures of mustard gas and its analogues with sodium thiomethoxide would at first sight seem to provide evidence for the presence of the related chloro-compound (VIII) in the original mixtures. In Parts I and II of this series, however, two routes have now been described by which (VI) can be formed from mustard gas; the isolation of small amounts of (VI) must not therefore be taken as proof of the presence of (VIII).

EXPERIMENTAL.

The Pyrolysis of 2 : 2′-*Dimethylthiodiethyl Sulphide* (I).—The thioether (redistilled, m. p. 24·3°; 40 to 80 g. in different experiments) was put into a 100 c.c. Claisen flask fitted with an 8-inch fractionating column (Vigreux type); it was then heated with a flame, the heating being adjusted to give a slow distillation (distillation temperature between 100° and 150°; initial liquid temperature *ca.* 250°). The heating was continued for 2½ hours, then the distillate and residue were combined and fractionated. The following fractions were isolated:

(*a*) Methylthiol was present in all experiments, and could be collected in a cold trap; yield 3—5 g. from 50 g. of (I). This compound was recognised by odour and b. p. (6°); by distillation into aqueous mercuric cyanide, mercury thiomethoxide was deposited [colourless plates from dioxan, m. p. and mixed m. p. 170° (decomp.)].

(*b*) The fraction, b. p. 40—80° [5—8 g. from 50 g. of (I)], on redistillation yielded *methyl vinyl sulphide* (IV), b. p. 69—70° (Found: S, 43·0. C_3H_6S requires S, 43·2%). This compound was a colourless oil, showing no signs of polymerisation on storage. It was mixed with phenylthiol (1 equiv.); reaction took place with evolution of heat, and was completed by heating at 100° for 15 minutes. Distillation of the product gave 1-*phenylthio*-2-*methylthioethane* as a colourless oil, b. p. 130°/3 mm.; yield, after one distillation, 80% (Found: S, 34·8. $C_9H_{12}S_2$ requires S, 34·8%). On oxidation with perhydrol and acetic acid, 1-*phenylsulphonyl*-2-*methylsulphonylethane* was deposited in 90% yield; colourless prisms from aqueous acetic acid, m. p. 172° (Found: S, 25·85. $C_9H_{12}O_4S_2$ requires S, 25·8%).

If this fraction, b. p. 40—80°, were left overnight before being redistilled it was found to contain 1 : 2-dimethylthioethane (VII), b. p. 60°/5 mm. (cf. Ewerlöf, *Ber.*, 1871, **4**, 716). This compound on oxidation with perhydrol and acetic acid gave 1 : 2-dimethylsulphonylethane, colourless plates from water, m. p. 190° (Found: S, 34·45. Calc. for $C_4H_{10}O_4S_2$: S, 34·4%). Otto, *loc. cit.*, gives m. p. 190°.

(*c*) A fraction, b. p. 40—125°/5 mm. [15 to 22 g. from 50 g. of (I)]. This apparently consisted of a large number of compounds, the separation of which proved difficult; nor were the results obtained in different experiments always the same. The following fractions were at one time or other obtained boiling over a fairly narrow range.

(i) A fraction, b. p. *ca.* 90°/55 mm., containing a thiol was always obtained. The SH value was variable, varying from 15·5% to 40·5% in different experiments; it is thought that the fraction consisted partly of 2-methylthioethylthiol (Moggridge, in the press); this compound requires SH, 30·5%; possible contaminants would be 1 : 2-dimethylthioethane (see above) and 1 : 2-dithioethane. In several experiments the α-naphthyl carbamate of 2-methylthioethylthiol, m. p. and mixed m. p. 119° (Moggridge, in the press), was isolated after treating the fraction with α-naphthyl *iso*cyanate.

(ii) A fraction, b. p. *ca.* 90°/5 mm., containing dithian, which crystallised in the condenser on re-distillation; m. p. and mixed m. p. 111° (cf. Masson, *J.*, 1886, **49**, 234). The remaining material in this fraction was never isolated in a state of purity.

(iii) In two experiments a fraction, b. p. 102—104°/2 mm., was obtained as a colourless oil (Found: S, 50·0%), giving on oxidation with perhydrol–acetic acid (cf. Part I) a sulphone, needles from water or glacial acetic acid, m. p. 168° (Found: S, 33·3%). The original compound did not reduce iodine; the sulphone was not soluble in aqueous alkali, and no satisfactory product could be isolated after the action of sodium ethoxide and methyl iodide; it therefore appeared that it did not contain a disulphonylmethane grouping. No sign of this compound was observed in later experiments; and further work on its structure was prevented by lack of material.

(*d*) (I), b. p. 135/5 mm., was recovered unchanged in all experiments; crude yield, 10—15 g. from 50 g. of starting material. It was identified by conversion into its sulphone, m. p. 265°.

(*e*) 1 : 2-Di-(2-methylthioethylthio)ethane (VI) was isolated from the distillation residue after several distillations followed by recrystallisations; yield of material, m. p. 64°, 0·03 g. from 50 g. of (I). The compound was identified by mixed m. p. with a synthetic specimen.

The authors wish to thank Dr. F. N. Woodward for his advice and encouragement.

RESEARCH ESTABLISHMENT, SUTTON OAK. [*Received, January* 23*rd*, 1946.]

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174. *The Methyl Thioethers derived from* 2 : 2′-*Dichlorodiethyl Sulphide and its Analogues. Part III. Synthetic Experiments.*

By R. BROWN and (the late) R. C. G. MOGGRIDGE.

The syntheses summarised in the schemes below have been carried out in order to confirm the structures of various compounds [*e.g.*, (III), (VI,), (IX), (X), (XIII), and (XVIII)] described in Parts I and II.

Various additions of thiols to vinyl sulphides, postulated in Part II, have been shown to occur spontaneously. The products have all been straight chain compounds, as opposed to the alternative possibility of the thioacetal type, RS·CHMe·SR′. The addition therefore proceeds to give the " abnormal " products: it thus falls into line with the addition of thiols to other classes of vinyl compound, when the " abnormal " products are usually obtained.

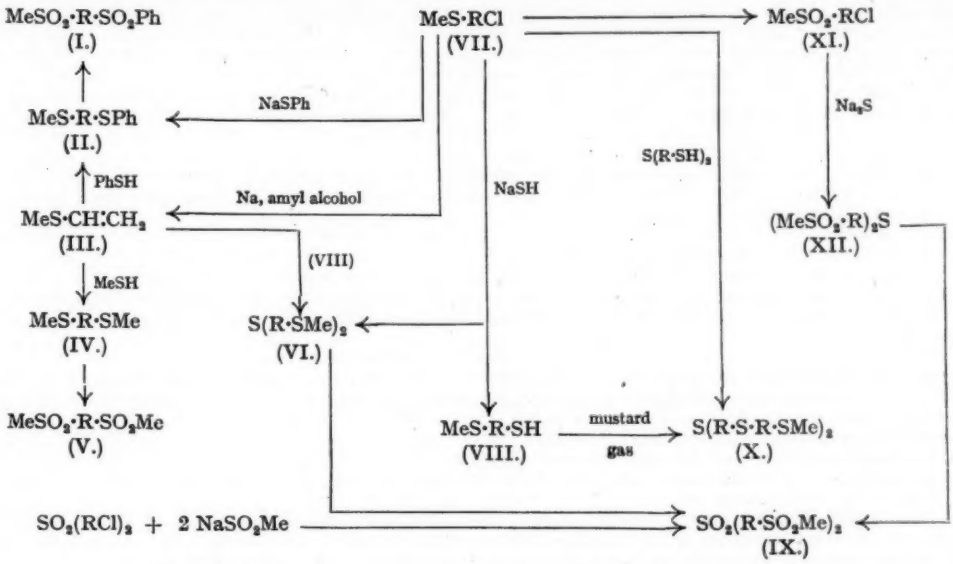
IN Part I (Meade and Moggridge, this vol., p. 813) it was found that the action of sodium thiomethoxide on 2 : 2′-dichlorodiethyl sulphide (" mustard gas ") gave, in addition to the expected product (VI), small amounts of (X) and (XIII). This result was so unexpected as to make desirable a direct synthetic confirmation of the structures of these compounds and of such related derivatives as (IX) and (XVIII). In addition, in Part II (Charnock and Moggridge, preceding paper) the spontaneous occurrence of several additions of thiols to vinyl compounds [*e.g.*, (III) to phenyl- and methyl-thiols, (III) to (VIII), (XVI) to (VIII)] was postulated; it was desirable to confirm their occurrence with synthetic specimens.

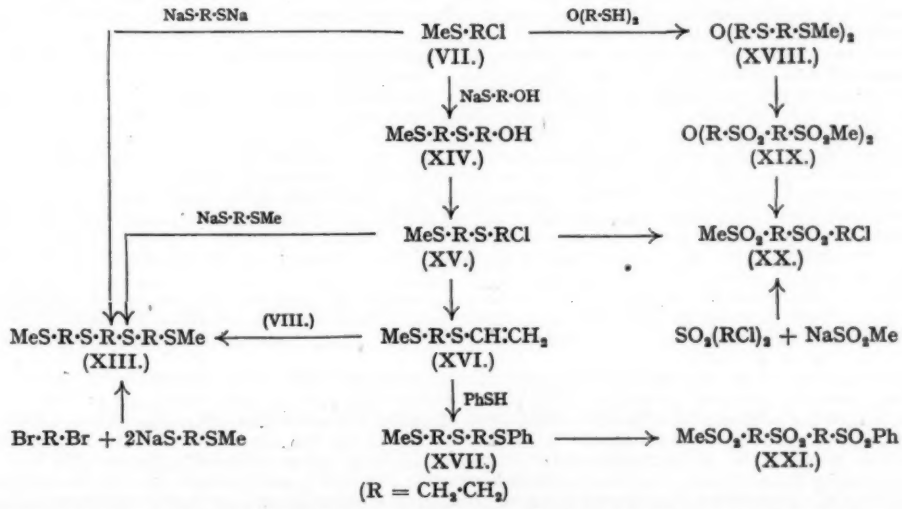
The following related schemes of synthesis were therefore undertaken (see opposite).

It is seen that the structures of the key compounds listed above are amply confirmed, (VI), (IX), and (X) by two syntheses, (XIII) by four, and (XVIII) by one synthesis and by the fission of its sulphone to give (XX). The products were in all cases identical with the compounds as prepared in the usual way.

Most of the reactions concerned were straightforward and call for little comment. Some [the formation of (VI) and (VIII) from (VII), and of (XX) from 2 : 2′-dichlorodiethyl sulphone and sodium methanesulphinate]

are to be described elsewhere (Moggridge, in the press) and are included in the schemes only for the sake of completeness.





The reactions of (III) with methyl- and phenyl-thiols and with (VIII), and of (XVI) with (VIII), were found to proceed smoothly and spontaneously at room temperature, as postulated in Part II. This reaction is of interest in that, as in general with vinyl compounds, the additions could in theory proceed in either of two ways; thus RSH + R′S·CH:CH$_2$ could give the straight chain products RS·CH$_2$·CH$_2$·SR′, or the thioacetal RS·CHMe·SR′. On grounds of electronic theory the second of these possibilities would be the " normal " reaction. Many authors (cf. *inter al.*, Read and Mayo, *Chem. and Ind.*, 1938, **16**, 752; Ipatieff, Pines, and Friedman, *J. Amer. Chem. Soc.*, 1938, **60**, 2731; Ipatieff and Friedman, *ibid.*, 1939, **61**, 71; Jones and Reid, *ibid.*, 1938, **60**, 2452) have, however, shown that thiols usually react with vinyl compounds to give the " abnormal " products unless special catalysts are added.

In this work the structure of the product of this reaction is definitely known in four cases; (II), (VI), and (XIII) are confirmed by other syntheses, while (IV) gives a sulphone (V) melting at 190° [Otto, *J. pr. Chem.*, 1887, **36**, 445, gives m. p. 190°; Baumann and Kast, *Z. physiol. Chem.*, 1890, **14**, 56, give m. p. 122° for the isomeric (MeSO$_2$)$_2$CHMe]. In all four cases the product is seen to be of the straight chain " abnormal " type. It appears therefore that, with regard to direction of addition of thiols, the alkyl vinyl sulphides fall into line with other classes of vinyl compound.

The opportunity is taken to describe the preparation of methyl 2-hydroxyethyl sulphide [required for the preparation of the corresponding chloro-compound, (VII)] from ethylene oxide and methylthiol; and also the fission of the sulphone (XIX) by hydrobromic and hydriodic acids to give the bromo- and iodo-analogues of (XX).

Experimental.

Methyl 2-Chloroethyl Sulphide (VII).—This was prepared from methyl 2-hydroxyethyl sulphide as described in *Org. Synth.* (Collective Vol. II, 136). The hydroxy compound was prepared either by the method given in *Org. Synth.* (Collective Vol. II, 345) or by the following method. Methylthiol (25 g.) was distilled into an ice-cooled mixture of ethylene oxide (22 g.) and methyl alcohol (200 c.c.) during one hour. The solvent was then removed by distillation, and the residue distilled to give the desired product, b. p. 63—64°/56 mm., in 75% yield.

Methyl Vinyl Sulphide (III).—Methyl 2-chloroethyl sulphide (25 g.) was refluxed for 30 minutes with a solution prepared from sodium (5·2 g.) and *n*-amyl alcohol (200 c.c.). The mixture was then distilled, and the material boiling below 135° collected and redistilled to give methyl vinyl sulphide in 50% yield, b. p. 69—70° (cf. Part II for its isolation after pyrolysis of 2 : 2′-dimethylthiodiethyl sulphide).

1-*Phenylsulphonyl*-2-*methylsulphonylethane* (I).—(*a*) Methyl vinyl sulphide (III) was treated with phenylthiol and the product oxidised with peracetic acid as described in Part II. The disulphone (I) was obtained, m. p. 172°, identical by mixed m. p. with that obtained in Part II.

(*b*) Methyl 2-chloroethyl sulphide (VII) (6·2 g.) was treated with a solution of sodium thiophenoxide, prepared from 36 c.c. of 1·67N-sodium ethoxide solution and 7·2 g. of phenylthiol; the mixture was kept for 10 minutes, and then refluxed for a further 10 minutes. Chloroform and dilute hydrochloric acid were then added, the chloroform layer separated, dried, and concentrated, and the residue distilled to give 1-phenylthio-2-methylthioethane (II) in 80% yield, b. p. 110°/0·5 mm., 115°/1 mm. Oxidation gave the disulphone (I) in 90% yield, identical by mixed m. p. with the two preceding preparations.

1 : 2-*Dimethylsulphonylethane* (V).—Excess of methylthiol was distilled into methyl vinyl sulphide (III) (1 g.) and the mixture was kept for some hours at room temperature. The crude 1 : 2-dimethylthioethane (IV) was, without further purification, treated with perhydrol–acetic acid, the solvent removed under reduced pressure, and the residue crystallised from water to give the disulphone (V) (0·7 g.), m. p. 190°. This was shown by mixed m. p. to be identical with the compound prepared as described in Part II.

2-*Methylthioethylthiol* (VIII) (cf. Moggridge, in the press).—The 2 : 2′-dimethylthiodiethyl sulphide (VI) obtained during this preparation was identified by oxidation to its trisulphone (IX), m. p. 264°, identical by mixed m. p. with a specimen prepared by the normal route.

2 : 2′-*Di*-(2-*methylthioethylthio*)*diethyl Sulphide* (X).—(*a*) 2-Methylthioethylthiol (VIII) (0·93 g.) was dissolved in sodium methoxide solution (from 0·2 g. of sodium), pure mustard gas (0·45 c.c., m. p. 14·3°) added, and the mixture refluxed for 10 minutes. Water (100 c.c.) was then added, and the crude product (1·0 g.), m. p. 72—77°, collected and crystallised from methyl alcohol. After one recrystallisation it melted at 84°, and was shown by mixed m. p. to be identical with the material prepared as in Part I.

This reaction was also carried out in aqueous media, the reactants being kept with occasional shaking for 30 minutes at room temperature and 30 minutes at 100°. Yield of (X), 60—70%.

(*b*) 2 : 2′-Dimercaptodiethyl sulphide (prepared from ethylene sulphide, Meade, private communication; cf. Meadow and Reid, *J. Amer. Chem. Soc.*, 1934, **56**, 2177) was dissolved in sodium methoxide solution (2 equivs.); methyl 2-chloroethyl sulphide (VII, 2 equivs.) was added, and the mixture refluxed for 30 minutes. The mixture was filtered hot; the filtrate on cooling deposited the required product, m. p. (after one crystallisation from alcohol) 84°. This compound was shown by mixed m. p. to be identical with that prepared by the other two methods.

Methyl 2-Chloroethyl Sulphone (XI).—Methyl 2-chloroethyl sulphide (VII; 9·0 g.) was treated with perhydrol (50 c.c.) and glacial acetic acid (50 c.c.). Heat was evolved. The mixture was kept overnight at room temperature, the solvents were then removed under reduced pressure, and the residue was distilled to give the required product in 72·5% yield; colourless oil, b. p. 112°/1 mm., m. p. 9° (Found: Cl, 24·9. Calc. for $C_3H_7O_2ClS$: Cl, 24·9%). Walter (*Ber.*, 1894, **27**, 3045) gives m. p. 9°.

2 : 2′-*Dimethylsulphonyldiethyl Sulphide* (XII).—The chlorosulphone (XI) was treated in the cold with an aqueous alcoholic solution of sodium sulphide (100% excess); the required *product* (XII) was then deposited in 96% yield. The yield became extremely low if the reaction mixture were heated. Long needles from water, m. p. 127° (Found: S, 38·9. $C_8H_{14}O_4S_3$ requires S, 39·0%).

2 : 2′-*Dimethylsulphonyldiethyl Sulphone* (IX).—(*a*) The disulphone (XII) on treatment with perhydrol–acetic acid in the usual way gave the required product in 65% yield; plates from aqueous acetic acid, m. p. 264°.

(*b*) Methanesulphinic acid was prepared by the action of sulphur dioxide on methylmagnesium iodide (cf. Boeseken and Ockenberg, *Rec. Trav. chim.*, 1914, **33**, 317). This reaction proceeded smoothly, and the magnesium salt of the required acid was obtained by concentration of its aqueous solution under reduced pressure. It was washed with alcohol, decomposed by the addition of sodium hydroxide solution (1 equiv.), and the sodium methanesulphinate obtained by concentration of the filtered solution under reduced pressure. A solution of 2 : 2′-dichlorodiethyl sulphone (1 equiv.) in aqueous alcohol was added; a crystalline solid was then deposited almost immediately. The mixture was refluxed for 15 minutes, cooled, and the product (IX) collected in 65% yield, m. p. 262°.

The products from both these syntheses were shown by mixed m. p. to be identical with the compound as prepared by direct oxidation of (VI) (cf. Part I).

2-*Hydroxy*-2′-*methylthiodiethyl Sulphide* (XIV).—To monothioethylene glycol (21·7 g.; cf. Bennett, *J.*, 1921, 423), dissolved in sodium ethoxide solution (from 6·25 g. of sodium), methyl 2-chloroethyl sulphide (VII; 30 g.) was added, and the mixture refluxed for 1 hour; after removal of sodium chloride and alcohol the residue was distilled to give the required *product* (XIV), 39 g., b. p. 125°/3 mm. (Found: S, 42·4. $C_5H_{12}OS_2$ requires S, 42·1%).

2-*Chloro*-2′-*methylthiodiethyl Sulphide* (XV).—The hydroxy-compound (XIV) (32 g.) in dry chloroform (150 c.c.) was treated with thionyl chloride (18·5 c.c.). The mixture was refluxed for 30 minutes after the initial vigorous reaction had subsided, and the solution was then decanted from some white gummy material and concentrated. Distillation of the residue gave the required *chloro*-compound (XV) as a colourless oil, b. p. 112°/3 mm., yield 30 g., which, on standing, slowly decomposed with deposition of a white solid (Found: Cl, 21·1; S, 36·85. $C_5H_{11}ClS_2$ requires Cl, 20·85; S, 37·55%).

2-*Methylthioethyl Vinyl Sulphide* (XVI).—To the chloro-compound (XV; 10 g.) in boiling alcohol, sodium ethoxide solution (from 1·35 g. of sodium) was added gradually during 15 minutes; the mixture was refluxed for a further hour, and sodium chloride and alcohol were then removed. Distillation of the residue gave the required *compound* (XVI) as a colourless oil showing no tendency to polymerise; b. p. 65°/2 mm. (Found: S, 47·3. $C_5H_{10}S_2$ requires S, 47·75%).

2-*Phenylsulphonyl*-2′-*methylsulphonyldiethyl Sulphone* (XXI).—The vinyl compound (XVI; 0·6 g.) and phenylthiol (0·485 g.) were mixed, and the initial reaction completed by heating at 100° in a sealed tube for 30 minutes. The crude thioether (XVII) without further purification was treated with perhydrol–acetic acid in the usual manner; the required *trisulphone* (XXI) was deposited; it crystallised from aqueous acetic acid in plates, m. p. 217° (yield, 85%) (Found: S, 28·15. $C_{11}H_{16}O_6S_3$ requires S, 28·25%).

1 : 2-*Di*-(2-*methylthioethylthio*)*ethane* (XIII).—(*a*) Ethylene dibromide (1·74 g.) was added to a solution of 2-methyl-

thioethylthiol (VIII; 2 g.) in sodium ethoxide solution (from 0·43 g. of sodium), and the mixture refluxed for 30 minutes. Sodium bromide was removed by filtration; the filtrate on cooling deposited the required product, m. p. 66·5°.

(*b*) Methyl 2-chloroethyl sulphide (VII; 0·41 g.) was added to a solution of ethylenedithiol [from ethylene sulphide (Meade, private communication), 0·38 g.] in sodium ethoxide solution (2 equivs.) and the mixture refluxed for 30 minutes. Chloroform and dilute acid were then added, and the chloroform layer was separated, dried, and concentrated under reduced pressure. The residue was purified by distillation and crystallisation to give the required product, m. p. 63°.

(*c*) 2-Chloro-2′-methylthiodiethyl sulphide (XV; 2·55 g.) was added to a solution of the thiol (VIII) (1·6 g.) in sodium ethoxide solution (from 0·34 g. of sodium), and the mixture was refluxed for 30 minutes. Sodium chloride was removed by filtration; the filtrate on cooling deposited the required product, m. p. (after recrystallisation from ethyl acetate–light petroleum) 64°.

(*d*) 2-Methylthioethyl vinyl sulphide (XVI; 1·24 g.) was cooled to 0° and the thiol (VIII; 1 g.), also at 0°, added. The mixture was kept overnight at room temperature; by morning it had set to a solid mass, and, after recrystallisation from ethyl acetate–light petroleum, gave the required product, m. p. 66·5°.

The products from each of these four syntheses were shown by mixed m. p. to be identical with the compound prepared as in Part I.

2 : 2′-*Di*-(2-*methylthioethylthio*)*diethyl Ether* (XVIII).—Methyl 2-chloroethyl sulphide (VII; 2 equivs.) was added to a solution of 2 : 2′-dithiodiethyl ether (Bäcker and Stienstra, *Rec. Trav. chim.*, 1933, **52**, 1038; one equiv.) in sodium ethoxide solution (*ca.* 2N; 2 equivs.) and the mixture refluxed for 30 minutes. Chloroform and dilute acid were then added, and the chloroform layer was separated, dried, and concentrated. The residue was distilled and subsequently crystallised from benzene–light petroleum; m. p. 35·5°, identical by mixed m. p. with the compound prepared as in Part I.

2-*Chloro*-2′-*methylsulphonyldiethyl Sulphone* (XX).—(*a*) 2-Chloro-2′-methylthiodiethyl sulphide (XIV) was oxidised as usual with perhydrol–acetic acid. The product (XX) was deposited in almost theoretical yield on cooling; needles from water, m. p. 162°.

(*b*) 2 : 2′-Di-(2-methylsulphonylethylsulphonyl)diethyl ether (XIX; cf. Part I) was recovered unchanged after being heated to 150° with concentrated hydrochloric acid for 4 hours. When, however, the compound (0·2 g.) was heated with glacial acetic acid (1 c.c.) and concentrated hydrochloric acid (1 c.c.) in a sealed tube at 200° for 4 hours, the chlorodisulphone (XX) was deposited in 80% yield on cooling, m. p. 160°.

The products from these two syntheses were shown by mixed m. p. to be identical with the compound as prepared from sodium methanesulphinate and dichlorodiethyl sulphone (Moggridge, in the press).

2-*Bromo*-2′-*methylsulphonyldiethyl Sulphone*.—2 : 2′-Di-(2-methylsulphonylethylsulphonyl)diethyl ether (XIX) was recovered unchanged after being heated to 150° for 4 hours with a mixture of glacial acetic and concentrated hydrobromic acids. When, however, the compound (4·2 g.) was heated at 200° for 3 hours with hydrobromic acid (16 c.c.; *d* 1·5) and bromine (1 c.c.), the required *bromo*-compound was deposited on cooling in 75% yield; needles from water or from glacial acetic acid, m. p. 185° (Found: Br, 28·65. $C_5H_{11}O_4BrS_2$ requires Br, 28·7%). On being warmed with pure pyridine the compound gave an insoluble *pyridinium* salt, which, after crystallisation from aqueous alcohol, had m. p. 245° (decomp.) (Found: Br, 22·9. $C_{10}H_{16}O_4NBrS_2$ requires Br, 22·4%).

2-*Iodo*-2′-*methylsulphonyldiethyl Sulphone*.—The tetrasulphone (XIX; 4 g.) and hydriodic acid (16 c.c.; *d* 1·7) were heated in a sealed tube to 150° for 4 hours; the *iodo*-compound was deposited on cooling; it crystallised from glacial acetic acid in plates, m. p. 219° (yield, 70%) (Found: I, 38·6; S, 19·4. $C_5H_{11}O_4IS_2$ requires I, 38·9; S, 19·6%). The *pyridinium* compound, prepared as for the bromo-derivative, had m. p. 220° (decomp.); mixed m. p. with the iodo-compound showed marked depression (Found: I, 31·0. $C_{10}H_{16}O_4NIS_2$ requires I, 31·3%).

The authors wish to thank Mr. R. J. Charnock for his assistance with part of this work, and Dr. F. N. Woodward for his advice and encouragement. They are indebted to the Chief Scientific Officer, Ministry of Supply, for permission to publish the work in this and the two preceding papers.

RESEARCH ESTABLISHMENT, SUTTON OAK. [*Received, January 23rd*, 1946.]

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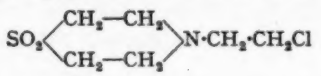
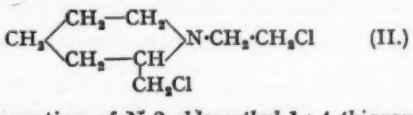
175. *Syntheses of some β-Chlorinated Amines.*

By A. H. FORD-MOORE, A. G. LIDSTONE, and WILLIAM A. WATERS.

Some analogues of 2 : 2′ : 2″-trichlorotriethylamine have been synthesised. The compounds have a physiological action similar to but less marked than that of the parent substance.

MANY β-chlorinated tertiary amines, such as 2 : 2′ : 2″-trichlorotriethylamine (McCombie and Purdie, *J.*, 1935, 1217) are known to be vesicant, whilst many quaternary salts containing the group $N{\cdot}CH_2{\cdot}CH_2X$ (X = $CO{\cdot}NH_2$ etc.) are highly toxic. In view of their relationship to, and derivability from, "mustard gas" and its

(I.) 



(II.)

toxic sulphone, the syntheses now described included the preparation of N-2-*chloroethyl*-1 : 4-*thiazan dioxide* (I), but it was found that the thiazan dioxide ring is not in itself a physiologically active group.

Whilst the simpler homologues of 2 : 2′ : 2″-trichlorotriethylamine had vesicant properties of a similar order, this physiological action is less marked in more complex compounds. A cyclic compound (II), analogous to an alkaloid, showed no outstanding toxic characteristics.

EXPERIMENTAL.

Di-(2-*chloroethyl*)*allylamine*.—Diethanolamine (15 g.), allyl bromide (15 g.), and anhydrous sodium carbonate (10 g.) were mixed, with cooling, and reaction was completed by warming on a water-bath for 2 hours. The product, diluted with alcohol, was filtered and fractionally distilled; *di*-(2-*hydroxyethyl*)*allylamine* was thus obtained as a colourless oil, b. p. 124°/2 mm. (Found: C, 58·2; H, 10·1. $C_7H_{15}O_2N$ requires C, 57·9; H, 10·0%). This was treated in chloroform

solution with a slight excess of thionyl chloride, and *di*-(2-*chloroethyl*)*allylamine* was isolated by basifying the reaction product and fractionating in a vacuum as a colourless liquid, b. p. 80°/3 mm. (Found: C, 46·5; H, 7·29; Cl, 39·1. $C_7H_{13}NCl_2$ requires C, 46·2; H, 7·14; Cl, 39·0%). On being kept it slowly turned brown, and deposited crystals of a dimer.

2-*Chloroethyldi*-(2-*chloro*-n-*propyl*)*amine*.—Ethanolamine (40 g.) and propylene oxide (70 g.) were mixed, with cooling, under reflux. After 12 hours, the mixture was heated to 100° for 2 hours and then cooled. A sticky mass of 2 : 2′ : 2″-trihydroxyethyldi-*n*-propylamine remained. Part of this was converted into the *hydrochloride* by treatment, under chloroform, with gaseous hydrogen chloride. The hydrochloride solidified after treatment with dry acetone, and was recrystallised from anhydrous alcohol, giving colourless crystals, m. p. 132° (Found: C, 45·3; H, 9·7; Cl, 16·3. $C_8H_{20}O_3NCl$ requires C, 45·0; H, 9·4; Cl, 16·7%). The remainder of the base was treated with twice its weight of thionyl chloride and diluted with chloroform (2 : 1), and reaction was completed by heating on the water-bath. After removing the solvent, the product was basified, extracted with chloroform, dried (Na_2SO_4), and distilled. 2-*Chloroethyldi*-(2-*chloro*-n-*propyl*)*amine* was obtained as a colourless oil, b. p. 117°/3 mm. (Found: C, 41·8; H, 7·1; Cl, 46·1. $C_8H_{16}NCl_3$ requires C, 41·3; H, 6·9; Cl, 45·9%). It formed a *picrate*, m. p. 117·5° (Found: C, 36·6; H, 3·8. $C_{14}H_{19}O_7N_4Cl_3$ requires C, 36·8; H, 3·1%), and a moderately soluble mercurichloride. On being kept the base darkened and gave a crystalline deposit of a dimer.

Di-(2-*chloroethyl*)-2-*chloro*-n-*propylamine*.—Diethanolamine (40 g.), propylene oxide (30 g.), and chloroform (50 c.c.) were mixed, with cooling, under reflux, and after a day the product was heated to 100° for 6 hours. Removal of the chloroform and excess of propylene oxide left a gummy mass of 2 : 2′ : 2″-trihydroxydiethyl-*n*-propylamine. Part of this was converted (as above) into the *hydrochloride* which crystallised from alcohol–ether in needles, m. p. 147° (Found: C, 42·2; H, 8·9; Cl, 17·8. $C_7H_{18}O_3NCl$ requires C, 42·1; H, 9·0; Cl, 17·8%). The remainder of the base was converted (as above) into *di*-(2-*chloroethyl*)-2-*chloro*-n-*propylamine*, which was a colourless oil, b. p. 114°/4 mm. (Found: C, 38·9; H, 6·4. $C_7H_{14}NCl_3$ requires C, 38·5; H, 6·4%). It gave a sparingly soluble mercurichloride, m. p. 143°.

N-*Methyl*-N-(2-*hydroxyethyl*)*morpholinium Iodide*.—*N*-(2-Hydroxyethyl)morpholine, b. p. 901°/3 mm., was obtained by heating together ethanolamine, 2 : 2′-dichlorodiethyl ether, and anhydrous potassium carbonate. It reacted with methyl iodide, with much heat evolution, to give a white solid *product* which crystallised from absolute alcohol in plates, m. p. 127° (Found: C, 30·8; H, 5·9. $C_7H_{16}O_2NI$ requires C, 30·8; H, 5·9%). Attempts to replace the hydroxyl group by chlorine were not successful.

N-2-*Hydroxyethyl*-1 : 4-*thiazan Dioxide Hydrochloride*.—Divinyl sulphone (24 g.) was added to a solution of ethanolamine (12 g.) in water (100 c.c.), and reaction was completed by refluxing for ½ hour. Hydrochloric acid (25 c.c.; *d* 1·16) was added, and the mixture was evaporated on a water-bath. On treatment with alcohol the residue crystallised, giving 39 g. (91% of theory) of the required product, which after recrystallisation from alcohol had m. p. 172° (Found: Cl′, 16·4. $C_6H_{14}O_3NClS$ requires Cl′, 16·4%). The *phenylurethane* of the base (from alcohol) had m. p. 110—111° (Found: C, 52·2; H, 5·91. $C_{13}H_{17}O_4NS$ requires C, 52·3; H, 6·08%).

N-2-*Chloroethyl*-1 : 4-*thiazan Dioxide Hydrochloride*.—The crude hydrochloride, prepared as above, was treated with pyridine (16 c.c.), and then warmed with a solution of thionyl chloride (20 c.c.) in chloroform (100 c.c.). After an hour the mixture was cooled and shaken with water, the chloroform layer was separated and dried, and the solvent was removed. The required product solidified on cooling. It crystallised from benzene–petroleum and had m. p. 63°. The *hydrochloride* crystallised from dilute alcohol, m. p. 188—189° (Found: Cl′, 14·9; hydrolysable Cl, 30·1. $C_6H_{13}O_2NCl_2S$ requires Cl′, 15·1; hydrolysable Cl, 30·3%).

Some of the free base was heated in a tube exposed in the vapours of boiling decalin; it melted and then resolidified, giving a *dimeric piperazinium salt* (Found: Cl′, 17·6. $C_{12}H_{24}O_4N_2Cl_2S_2$ requires 17·9%).

NN-*Di*-(2-*chloroethyl*)*piperidinium Chloride*.—*N*-(2-Hydroxyethyl)piperidine (cf. Leffler and Brill, *J. Amer. Chem. Soc.*, 1933, **55**, 365; Tullock and McElvain, *ibid.*, 1939, **61**, 961) and ethylene chlorohydrin were heated on a water-bath for 12 hours. The product, *di*-(2-*hydroxyethyl*)*piperidinium chloride*, was ground with acetone, filtered off, washed with acetone, and so obtained as very deliquescent crystals, m. p. 192—193° (Found: Cl′, 16·8. $C_9H_{20}O_2NCl$ requires Cl′, 16·9%). This salt (17·5 g.), thionyl chloride (15 c.c.), and chloroform (50 c.c.) were heated for 2 hours on the water-bath. Solvent was removed, and the residue was ground with cold acetone and filtered off. It crystallised from the minimum quantity of boiling 98% alcohol in colourless, very deliquescent plates of *di*-(2-*chloroethyl*)*piperidinium chloride monohydrate*, m. p. 218° (decomp.) [Found: Cl′, 13·5; loss of wt. at 110°, 5·8. $(C_9H_{18}NCl_2)^+Cl^-,H_2O$ requires Cl′, 13·4; H_2O, 6·8%].

dl-2-*Chloromethyl*-N-(2-*chloroethyl*)*piperidine* (II).—Ethyl *dl*-pipecolinate was prepared by catalytic reduction of picolinic acid hydrochloride and esterification of the product. It was reduced with sodium and alcohol to *dl*-2-hydroxymethylpiperidine (m. p. 75°; b. p. 100—102°/6 mm.), which was then refluxed with ethylene chlorohydrin and potassium carbonate in alcohol. This gave *dl*-2-hydroxymethyl-*N*-(2-hydroxyethyl)piperidine as a thick oil, b. p. 142—145°/3 mm., which could not be induced to solidify. Its *picrate*, prepared in benzene solution, crystallised from acetone–petrol (Found: C, 43·3; H, 5·01; N, 14·2. $C_{14}H_{20}O_9N_4$ requires C, 43·3; H, 5·15; N, 14·4%).

The free base was treated with thionyl chloride in chloroform solution. Removal of the solvent left a dark coloured residue which was extracted 3 times with ether; the remaining solid was then recrystallised from acetone giving dl-2-*chloromethyl*-N-(2-*chloroethyl*)*piperidine hydrochloride*, m. p. 145° (Found: Cl′, 15·4. $(C_8H_{16}NCl_2)^+Cl^-$ requires Cl′, 15·4%). The corresponding base was prepared only in benzene solution.

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CHEMICAL DEFENCE RESEARCH DEPARTMENT, MINISTRY OF SUPPLY. [*Received, February 14th*, 1946.]

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176. *The Preparation of Simple Organic Orthoborates.*

By LEO H. THOMAS.

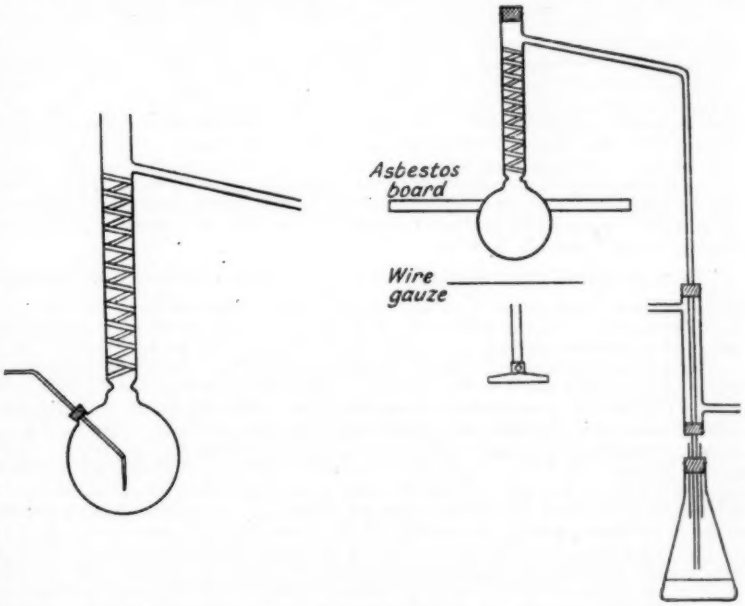
The synthesis of a number of organic orthoborates has been undertaken with a view to ascertain the most convenient and economical methods of preparation. The preparation of nine hitherto unknown borates is described.

ESTERS of orthoboric acid are of some importance on account of their unique electronic structure (Yabroff, Branch, and Almquist, *J. Amer. Chem. Soc.*, 1933, **55**, 2935). In recent years patents have been taken out covering their use as plasticisers for natural and synthetic resins and cellulose derivatives, as emulsifying agents and coating compositions, and as pharmaceutical and antiseptic preparations (U.S.PP. 1936, 2,053,474; 1941,

2,223,349; Fr.P. 1939, 848,459). It has also been stated that alkyl borates may with advantage replace alkyl chlorides in the Friedel–Crafts reaction (D.R.-P. 1930, 555,403).

The most useful methods for preparing boric esters are: (1) By refluxing a mixture of boric oxide and an alcohol with an inert solvent such as toluene, and allowing the condensed vapours to percolate through anhydrous copper sulphate held in the thimble of a Soxhlet extractor to remove the water formed during the reaction (Dupire, *Compt. rend.*, 1936, **202**, 2086). (2) By azeotropic removal of the water of reaction (Johnson and Tomkins, *Org. Synth.*, 1933, **13**, 16). (3) By alcoholysis (Schiff, *Annalen*, Suppl., 1867, **5**, 183; Wuyts and Duquesne, *Bull. Soc. chim. Belg.*, 1939, **48**, 77).

Method (1) is the most convenient for preparing quantities of 20—100 g., and it has been extended to the preparation of aryl borates. For the preparation of larger amounts, it is best, where possible, to employ method (2). In the case of alkyl borates, the water is removed continuously as a binary azeotrope with the alcohol used. This involves the use of slight excess of the alcohol. (Alternatively, a subsidiary inert liquid such as benzene, toluene, or carbon tetrachloride may largely replace the excess alcohol.) The water is then removed as a ternary azeotrope composed of water, the alcohol, and the subsidiary liquid. The method has been successfully employed by the author for the preparation of aryl borates which hitherto have been prepared by less convenient methods. In this case subsidiary liquids such as toluene and xylene possessing a b. p. higher than that of water are best used, the water being removed by distillation with the toluene or xylene.



Method (3) can be employed in the preparation of those borates which cannot be obtained by methods (1) and (2). For instance, β-aminoethyl alcohol does not react with boric anhydride under the conditions prevailing in methods (1) and (2). However, *β-aminoethyl borate* has been prepared simply by distilling a mixture of the ethanolamine with the borate of a more volatile alcohol, *e.g.*, tri-*n*-propyl borate, according to the equation

$$B(OR)_3 + 3NH_2\cdot CH_2\cdot CH_2\cdot OH = B(O\cdot CH_2\cdot CH_2\cdot NH_2)_3 + 3ROH$$

The reaction was employed by Wuyts and Duquesne (*loc. cit.*), who distilled a mixture of the alcohol or phenol with a 25% excess of *n*-propyl borate. The bulk of the propyl alcohol was removed by distillation at atmospheric pressure, and the last traces together with the excess of propyl borate at reduced pressure. In the present work, a slight excess of the alcohol or phenol has been used in place of the excess of borate.

Experimental.

Distillation flasks of special design having advantages over the usual type were used (see Fig.). They had long necks fitted with solid glass spirals. The bulbs carried side tubes in which air leaks could be placed. Some of the borates possessed high m. p.'s, and so tended to crystallize out in the side arm during distillation. Accordingly, some of the flasks were fitted with wide side arms to prevent obstruction.

The boron content in aryl borates and in those containing basic or acidic groups could not be determined in the usual way by titration against sodium hydroxide in the presence of glycerol, owing to the acid or basic nature of the liberated phenol or alcohol. For such borates, the following method was found satisfactory. A known weight of the borate was washed into a distillation flask of the type described above with 50 c.c. of pure methyl alcohol containing two drops of pure concentrated sulphuric acid. About 20 c.c. were distilled over through a condenser into a receiving flask which contained 50 c.c. of boiled-out distilled water. After addition of glycerol or mannitol, the contents of the receiver were titrated against carbonate-free sodium hydroxide with phenolphthalein as indicator in the usual way. The process was then repeated, a second 10 c.c. being distilled off, and the contents of the flask again titrated. In this way it was found that the first distillation brought over nearly all of the boron as an azeotrope of methyl alcohol and methyl borate. The process was again repeated if necessary until no more sodium hydroxide was required to neutralise the boric acid formed in the receiver.

To determine whether or not sulphuric acid was carried over under these conditions, the process was conducted in the absence of a borate. A distillate of 50 c.c. was found to be absolutely neutral.

The analytical results for *cyclo*hexyl borate, known to be pure from the usual method of analysis, is given as proof of the accuracy of the above method:

Weight of *cyclo*hexyl borate taken, g., 0·3505.
Total volume of distillate, c.c., 20, 30, 40.
Total volume of 0·07092N-NaOH needed, c.c., 15·80, 15·95, 16·00.
Boron found, 3·50%. Boron calculated, 3·51%.

The following borates have not hitherto been prepared.

1-*Methylisoamyl* (*Methylisobutylcarbinyl*) *Borate*, $B(O{\cdot}CHMe{\cdot}CH_2{\cdot}CHMe_2)_3$.—10·5 G. of boric anhydride (1 mol.), 92 g. (6 mols.) of methyl*iso*butylcarbinol (b. p. 130—131°), and 100 c.c. of pure benzene were placed in a round-bottomed flask fitted with a Soxhlet extractor, a condenser, and thermometer placed so as to register the temperature of the vapours. 40 G. of anhydrous copper sulphate were placed in the Soxhlet. In place of the usual thimble, it was found that a plug of glass wool at the bottom of the Soxhlet sufficed to retain the copper sulphate.

After 4—5 hours of refluxing, the temperature had risen from 72° to a constant value at 80°. This indicated almost complete disappearance of the hexyl alcohol, and completion of reaction. After removal of the benzene by distillation at atmospheric pressure, the reaction mixture was fractionated under reduced pressure. This gave 84 g. (90%) of the required *borate*, b. p. 130—131°/17 mm. It is a clear colourless liquid. In common with all the organic orthoborates examined, it is hygroscopic and readily hydrolysed by atmospheric moisture (Found: B, 3·44. $C_{18}H_{39}O_3B$ requires B, 3·44%).

β-Methylallyl Borate, $B(O{\cdot}CH_2{\cdot}CMe{:}CH_2)_3$.—This ester was similarly prepared from 14 g. of boron trioxide, 90 g. of β-methylallyl alcohol (b. p. 112—113°), 130 c.c. of toluene, and 40 g. of anhydrous copper sulphate. After 3 hours' heating, the temperature had risen from 83° to 110° (constant). The toluene was removed by distillation through an eight-pear column, and the residue fractionated to give 80 g. of *borate*, b. p. 220—226°. It solidified on cooling to a mass of colourless crystals, m. p. 28—29° (Found: B, 4·80. $C_{12}H_{21}O_3B$ requires B, 4·83%).

p-Chlorophenyl Borate.—In this case reaction was slow. 12 G. of boric anhydride (1 mol.), 128 g. (6 mols.) of *p*-chlorophenol, and 130 c.c. of toluene were refluxed through 50 g. of anhydrous copper sulphate for 15 hours, until the thermometer registered 100°. Fractionation under reduced pressure yielded 47 g. of unreacted *p*-chlorophenol and 50 g. (38%) of *p-chlorophenyl borate*, b. p. 258—260°/5 mm., as a highly viscous, pale green liquid which slowly solidified to a mass of crystals, m. p. 60—64° (Found: B, 2·73. $C_{18}H_{12}O_3Cl_3B$ requires B, 2·75%).

p-Methoxyphenyl Borate.—This was similarly prepared from 2·4 g. of trioxide, 25 g. of *p*-methoxyphenol, and 100 c.c. of benzene. The mixture was refluxed for 7 hours, and then fractionally distilled, yielding 10 g. (40%) of *borate*, b. p. 288°/7 mm. The product solidified on cooling to a mass of colourless crystals, m. p. 43—45° (Found: B, 2·81. $C_{21}H_{21}O_6B$ requires B, 2·84%).

Tri-o-phenylene Diborate, $C_6H_4(O{\cdot}B\langle{}^{O}_{O}\rangle C_6H_4)_2$.—23 G. of boric anhydride, 110 g. of catechol, and 200 c.c. of toluene were refluxed through 80 g. of anhydrous copper sulphate until the thermometer registered a constant temperature of 110° (6 hours). On fractionation, 80 g. (68%) of the *borate* were obtained, b. p. 240—242°/7 mm. It solidified to a mass of colourless crystals, m. p. 99—104° (Found: B, 6·18. $C_{18}H_{12}O_6B_2$ requires B, 6·20%).

1-*Carbo*-n-*propoxyethyl Borate*, $B(O{\cdot}CHMe{\cdot}CO_2Pr)_3$.—This was prepared in a rather impure condition from 10 g. of boric anhydride (1 mol.), 113 g. (6 mols.) of *n*-propyl lactate, 150 c.c. of benzene, and 40 g. of anhydrous copper sulphate in the usual way (constant temperature of 80° after 12 hours). A fraction consisting of impure borate, b. p. 160—175°/5 mm., was obtained on distillation. It was redistilled over 2—3 g. of solid sodium hydroxide, and 20 g. of the *borate* were collected at 169—175°/5 mm., as a colourless viscous liquid. Boron was determined by the method describd above (Found: B, 2·73. $C_{18}H_{33}O_9B$ requires B, 2·67%). Then 0·4563 g. of ester was dissolved in cold water and titrated against 0·07092N-sodium hydroxide using phenolphthalein as indicator in the presence of glycerol. Titration was then continued in the hot, the alkali being added 0·5 c.c. at a time, until a permanent red colour was obtained. This extra alkali, *i.e.*, that necessary to hydrolyse the propyl lactate, was 46 c.c. (Calc. 48 c.c.).

p-*Tolyl Borate*.—A mixture of 11·7 g. of boric anhydride (1 mol.), 108 g. of *p*-cresol (6 mols.), and 200 c.c. of toluene was slowly distilled through an eight-pear column. Successive 100-c.c. portions were taken off, the top layer being each time returned to the reaction vessel. After 5—7 distillations, the volume of water brought over reached the theoretical volume of 9 c.c., and all the boron oxide had disappeared. The reaction mixture on fractionation gave 89 g. of p-*tolyl borate*, b. p. 248—250°/12 mm. It slowly set to a mass of pale yellow crystals, m. p. 58—61° (yield, 80%) (Found: B, 3·28. $C_{21}H_{21}O_3B$ requires B, 3·26%).

β-Aminoethyl Borate.—94 G. of *n*-propyl borate were mixed with 120 g. of ethanolamine in a flask fitted with a one-foot column. Slow distillation gave 105 c.c. of distillate, b. p. 99—105°. The residue was fractionated to yield 58 g. of *β-aminoethyl borate*, b. p. 126—127°/8 mm. It quickly solidified to a mass of colourless crystals, m. p. 95—98° (yield, 60%) [Found: NH_2, 25·4. $C_6H_{12}BO_3(NH_2)_3$ requires NH_2, 25·1%]. The amino-groups were determined by titration against hydrochloric acid with methyl-red as indicator.

o-*Chlorophenyl Borate*.—This was prepared by a variation of method (3), for *o*-chlorophenol does not react with boric anhydride. 12 G. of boric anhydride, 128 g. (6 mols.) of *o*-chlorophenol, 73 c.c. of *n*-propyl alcohol, and 130 c.c. of toluene were refluxed through 50 g. of anhydrous copper sulphate for 3—4 hours until the thermometer reading was constant. The product was then distilled through a column to remove toluene and propyl alcohol, and the residue fractionated in a vacuum. 45 G. of o-*chlorophenyl borate* were collected at 242°/6 mm. as a viscous oil which slowly solidified to a mass of colourless crystals, m. p. 47—49° (yield, 34%) (Found: B, 2·70. $C_{18}H_{12}O_3Cl_3B$ requires B, 2·73%).

An attempt was made to prepare the borate of *o*-acetamidophenol by distilling slowly a mixture of 25 g. of the phenol and 40 c.c. of *n*-propyl borate, from an oil-bath heated to 160—190°. Some 10 c.c. of *n*-propyl alcohol distilled off at 96—99°, followed by a second fraction at 170—200°. The latter fraction was washed with three 100-c.c. portions of water to remove unchanged propyl borate. 18 G. of a colourless heavy oil remained; b. p. 203—205°. When a solution of this in dilute hydrochloric acid was kept for several hours, a crystalline precipitate of *o*-acetamidophenol, m. p. 202—204°, separated. The heavy oil was therefore identified as 2-methylphenoxazole, so alkyl borates may possibly be used with advantage as mild reagents for bringing about condensations attended by the elimination of water.

tert.-Alkyl borates cannot be prepared by the above methods.

All the borates considered above are freely soluble in benzene, toluene, ether, carbon tetrachloride, and acetone. Those borates which are liquid at room temperature are immiscible with water, but are more or less rapidly hydrolysed by it, the primary alkyl borates much more readily than secondary.

Owing to this sensitivity to moisture, sharp m. p.'s could not easily be obtained for the solid borates. The following proved to be the most satisfactory method. A few large crystals were transferred as rapidly as possible to the bottom of a dried narrow test-tube, and powdered by means of a glass rod. The tube was then drawn out to a 2-mm. diameter capillary, care being taken not to melt the sample. The capillary was broken at a convenient point, the tube sealed off, allowed to cool, and the dry crystals shaken down into the capillary. The m. p. was then determined in the usual way. Whenever possible, the m. p. so obtained was confirmed by the cooling-curve method on the bulk sample. Such a procedure was rarely practicable on account of the high degree of supercooling characteristic of most of the borates.

SCHOOL OF MINES AND TECHNOLOGY, TREFOREST. [*Received, February 7th*, 1946.]

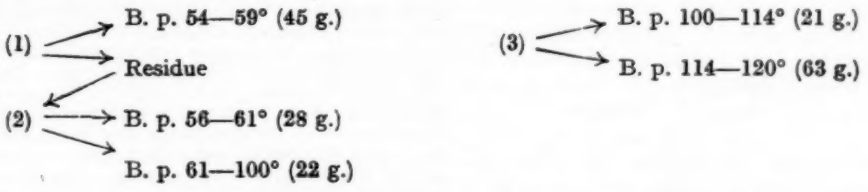
177. *The Preparation of Mixed Organic Orthoborates.*

By Leo H. Thomas.

The preparation and properties of a number of mixed organic orthoborates are described. They have been found to "disproportionate" with great readiness.

Schiff (*Annalen*, Suppl., 1867, **5**, 183) claimed to have prepared diethyl amyl and ethyl diamyl borates by heating together either monoethyl borate with amyl alcohol or amyl borate with ethyl borate, and to have obtained methyl diethyl borate by heating monomethyl borate with ethyl alcohol. Similar experiments have now been carried out, the following being typical.

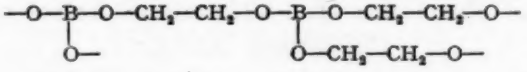
A mixture of *n*-propyl alcohol and *n*-amyl alcohol (3 g.-mols. of each) was converted into 240 c.c. of mixed borates by refluxing with benzene and boric anhydride under the conditions of Method (1) (preceding paper). The mixture so obtained was carefully fractionated under 16 mm. through a two-foot Hempel column into the following fractions: (1) 90—103°, 76 c.c.; (2) 103—135°, 48 c.c.; (3) 135—150°, 102 c.c. Each of these fractions was then separately distilled under the same conditions, but at 5 mm. The results are shown schematically below:



Fractions of b. p. 54—61°/5 mm. and 100—120°/5 mm. were found by distillation at ordinary pressure to be almost pure tri-*n*-propyl and -*n*-amyl borate, respectively. The middle fraction, b. p. 61—100°/5 mm., on redistillation under 5 mm. gave: (*a*) b. p. 70—100° (11 g.), (*b*) b. p. 100—115° (26 g.). It can be seen therefore that, although the middle fractions are persistent, their weight steadily becomes less during efforts to isolate the pure mixed borates.

A similar experiment with phenol and *n*-propyl alcohol (3 g.-mols. of each) gave 35 g. of propyl borate, b. p. 80°/18 mm., and 35 g. of phenyl borate, b. p. 190—205°/6 mm., only a few c.c. of intermediate product being obtained. It seems likely, therefore, that two simple borates $B(OR)_3$ and $B(OR')_3$ interact rapidly to give a mixture of all four possible compounds, *viz.*, these two and $B(OR)(OR')_2$ and $B(OR)_2(OR')$. Clearly, the possibility of isolating a pure mixed borate depends on the speed with which it is rearranged on distillation; *e.g.*, $B(OR)(OR')_2 \longrightarrow B(OR')_3 + B(OR)_3 + B(OR)_2(OR')$, and hence Schiff's claim to have isolated pure mixed borates rested on fortuitous analysis of the appropriate distillation cuts.

The mixed borates of the type considered above have, of necessity, b. p.'s intermediate between those of the corresponding simple borates, but on substitution of a suitable dihydroxy-compound in place of a monohydric alcohol, this would no longer be true. With catechol and *cyclo*hexyl alcohol, for example, the following mixed borates are possible: $B(C_6H_{11}O)_3$, $B_2(C_6H_4O_2)_3$, and $C_6H_{11}O{\cdot}B\langle{}^{O}_{O}\rangle C_6H_4$. Because of its much lower molecular weight, the mixed borate would possess the lowest b. p., and it should be possible to distil it out from the equilibrium mixture as it is being formed. This proved to be the case, and a number of such mixed borates have been prepared in pure condition. It must be presumed, however, that the mixed borates so obtained more or less rapidly revert to the equilibrium mixture of composition dependent on the prevailing temperature. This conclusion is supported by the fact that cyclo*hexyl ethylene borate*, b. p. 119°/10 mm., a mobile liquid, on cooling sets to a glassy, almost non-flowing solid. It could not be induced to crystallize. The plastic nature of the borate is probably due to the formation of long chains as a result of this interconversion:



Those borates prepared from 1 : 2-glycols are glassy solids (Dupire, *Compt. rend.*, 1936, **202**, 2096). cyclo*Hexyl o-phenylene borate*, on the other hand, is a crystalline solid, for the phenylene borate formed on rearrangement is a crystalline solid.

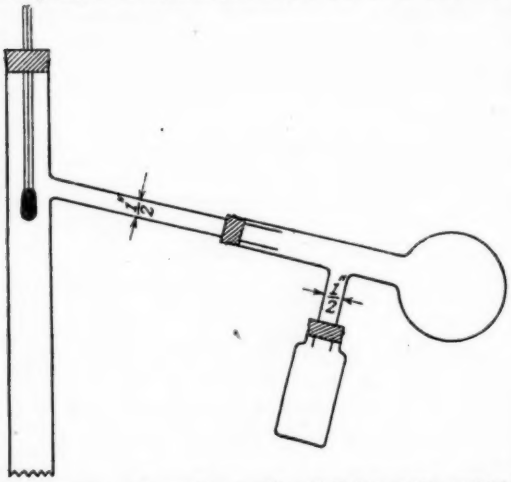
Radical interchange has been observed in the case of alkyl orthoformates by Post and Erickson (*J. Amer. Chem. Soc.*, 1933, **55**, 3851), who, by the action of 1 equiv. of chloroform on 1·5 equivs. each of two aliphatic alcohols, obtained the mixed orthoformates. Here the speed of disproportionation was such that the mixed esters could be separated by fractional distillation. On standing for one month, a mixture of tri-*n*-propyl and tri*iso*amyl orthoformate gave rise to the mixed orthoformates.

The high speed with which the mixed borates disproportionate might be considered to place the reaction in the category of tautomerism.

Experimental.

Phenyl o-Phenylene Borate, $C_6H_5\cdot O\cdot B\langle{}^{O}_{O}\rangle C_6H_4$.—An equimolecular mixture of 17·5 g. of boric anhydride, 47 g. of phenol, and 55 g. of catechol was made up in 300 c.c. of toluene. The water formed in the reaction was removed by co-distillation with the toluene. 150 C.c. of toluene were distilled off through a column, separated from the water, and returned to the reaction vessel. After 5 such distillations, 14·5 g. of water had been eliminated from the reaction mixture. The residue on fractionation under reduced pressure, gave 64 g. of *phenyl o-phenylene borate*, b. p. 166—167°/12 mm., the temperature then rising sharply. The mixed borate solidified on cooling to a white crystalline mass, m. p. 40—44° (yield 60%) (Found: B, 5·12. $C_{12}H_9O_3B$ requires B, 5·10%).

cyclo*Hexyl Ethylene Borate*, $C_6H_{11}\cdot O\cdot B\langle{}^{O}_{O}\rangle C_2H_4$.—An equimolecular mixture of 17·5 g. boron oxide, 50 g. of *cyclo*hexanol, and 31 g. of ethylene glycol (1 mol.) in 200 c.c. of toluene was distilled, and the condensed vapours allowed to percolate through 40 g. of anhydrous copper sulphate (see preceding paper). At the end of 5 hours, the temperature of the vapours had become constant at 110°. After removal of the toluene by distillation at ordinary pressure, the reaction product was fractionated in a vacuum through an eight-pear column. A small quantity distilled at 78—82°/14 mm., after which the temperature rose sharply to 119°/10 mm., where 51 g. (60%) of cyclo*hexyl ethylene borate* were collected (Found: B, 6·30. $C_8H_{15}O_3B$ requires B, 6·32%).



Great difficulty was experienced in collecting the mixed borate, because it set to a non-flowing, transparent, colourless, glassy mass on the cooler parts of the receiver and the column side arm; a condenser could not be employed. The difficulty was minimised by using as receiver a distillation flask with a wide side tube carrying a bottle (see Fig.). The first distillate was allowed to collect in the bulb of the receiver, the borate being then collected in the bottle by turning the flask into the correct position. The vapours were condensed, after the first few c.c. of the borate had collected, by wrapping a wet cloth around the side arm of the column. This procedure was just sufficient to condense the mixed borate to a warm liquid not too viscous to flow into the bottle.

cyclo*Hexyl o-Phenylene Borate*.—This was similarly prepared from 9 g. of boron oxide, 25 g. of *cyclo*hexanol, and 27·5 g. of catechol, 30 g. of anhydrous copper sulphate and 150 c.c. of benzene being used. At the end of 6 hours, the temperature had become constant at 80°. The benzene was removed at ordinary pressure, and the residue fractionated in a vacuum. A small quantity distilled at 75—120°/20 mm., and sharp separations were obtained of the mixed borate (24 g., b. p. 168°/20 mm.) and phenylene borate (12 g., b. p. 252°/14 mm.). The mixed *borate* set to a white mass of crystals, m. p. 55—59° (yield 44%) (Found: B, 4·91. $C_{12}H_{15}O_3B$ requires B, 4·96%).

n-*Amyl Ethylene Borate*.—This was prepared in the same way as the *cyclo*hexyl ethylene ester (12 g. of boric anhydride, 29 g. of *n*-amyl alcohol, 21 g. of ethylene glycol, 150 c.c. of toluene, 35 g. of copper sulphate). The temperature became constant at 110° after 6 hours' refluxing. The toluene was distilled off through an eight-pear column, and the residue fractionated in a vacuum: 10 c.c. came over at 70—90°/18 mm., after which the temperature rose sharply, and 28 g. of the mixed *borate* were collected at 108—110°/14 mm. The sample was somewhat impure (Found: B, 6·70, 6·72. $C_7H_{15}O_3B$ requires B, 6·84%); on redistillation, 16 g., b. p. 106°/12 mm. (Found: B, 6·80%), were obtained. On cooling, it set to an extremely viscous colourless liquid.

Phenyl Ethylene Borate.—17·5 G. of boron oxide, 47 g. of phenol, 31 g. of ethylene glycol, and 200 c.c. of benzene were refluxed for 7 hours in the usual way through 40 g. of anhydrous copper sulphate. The product was distilled at ordinary pressure, and the mixed *borate* collected at 250—268°. Redistillation gave 40 g., b. p. 262—268°. As analysis showed the sample to be impure, it was redistilled under reduced pressure; 12 g. were collected, b. p. 123—127°/5 mm. On cooling, it set to a transparent, colourless, glassy solid (Found: B, 6·78. $C_8H_9O_3B$ requires B, 7·07%).

The phenol was determined by titration with potassium bromate in the presence of potassium bromide and hydrochloric acid (Found: C_6H_5, 43·6. $C_8H_9O_3B$ requires C_6H_5, 46·9%).

In the foregoing work, distillation of the final products was conducted in the special flasks described in the preceding paper, and analysis of those borates containing aryl groups was carried out in the manner there outlined.

School of Mines and Technology, Treforest. [*Received, February 7th*, 1946.]

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178. *Preparation and Properties of 2-Chloroalkyl Esters of Boric, Silicic, and Phosphoric Acids.*

By W. J. Jones, L. H. Thomas, E. H. Pritchard, and S. T. Bowden.

Improved methods are described for the preparation of 2-chloroalkyl esters of ortho-boric, -silicic, and -phosphoric acids. The physical properties of these esters have been examined. Parachor measurements reveal that the values of the parachor constants of boron and silicon depend upon the molecular weight and complexity of the compound under investigation.

The first halogenoalkyl borate was prepared by Councler (*J. pr. Chem.*, 1878, **18**, 380), who obtained tri-2 : 3-dibromopropyl borate by the action of bromine on triallyl borate. In a study of the action of bleaching powder and boric acid on dimethylpentanol, Pastureau and Veiler (*Compt. rend.*, 1936, **202**, 1683) obtained the boric ester of the chlorohydrin of dimethylpentanol, which was also prepared by the action of boric acid on the chlorohydrin of tetramethylglycerol; the latter method was further used for the preparation of the

boric esters of the chlorohydrins of trimethylethylglycerol and dimethyldiethylglycerol. Dupire (*ibid.*, p. 2086) prepared boric esters by refluxing mixtures of the appropriate alcohol, boric acid, and toluene, and removing water from the condensed vapours by means of anhydrous copper sulphate. By this method, which is claimed to avoid the formation of esters of metaboric acid, Dupire was able to prepare the boric ester of 1-chloro-2 : 3-dihydroxypropane. Through the interaction of chloral and triethylborine, Meerwein, Hinz, Majert, and Sönke (*J. pr. Chem.*, **1937**, **147**, 226) prepared the trichloroethyl ester of diethylboric acid, while Meerwein, Hinz, Hofmann, Kroning, and Pfeil (*ibid.*, p. 257) obtained similar halogenated derivatives of boric esters by the action of boron trifluoride etherate upon epichlorohydrin.

Employing a modification of the method of Dupire (*loc. cit.*), we have prepared *tri-2-chloroethyl orthoborate*, $B(O{\cdot}CH_2{\cdot}CH_2Cl)_3$, and *tri-2 : 2′-dichloroisopropyl orthoborate*, $B[O{\cdot}CH(CH_2Cl)_2]_3$. These esters are colourless liquids with little odour, and the *iso*propyl derivative is highly viscous. Both liquids are readily hydrolysed by moisture with formation of the corresponding chlorohydrin and boric acid. Parachor measurements reveal that the parachor constants of boron in these esters are 21·6 and 37·1, respectively. Inasmuch as the parachor constants of this element in simple alkyl orthoborates (Sugden, " The Parachor and Valency," London, 1930, p. 187) range from 15·9 to 17·8, it appears that the observed value of the constant rises with increasing molecular weight and complexity of the boron compound.

The two chloroalkyl orthosilicates hitherto prepared are those of tetra-2-chloroethyl $Si(O{\cdot}CH_2{\cdot}CH_2Cl)_4$ and tetra-2-chloro*iso*propyl $Si[O{\cdot}CH(CH_2Cl){\cdot}CH_3]_4$, which were obtained by Taurke (*Ber.*, 1905, **38**, 1667) by the action of silicon tetrachloride on the appropriate glycol or chlorohydrin. Dearing and Reid (*J. Amer. Chem. Soc.*, **1928**, **50**, 3058) also prepared tetra-2-chloroethyl orthosilicate of 94% purity through interaction of silicon tetrachloride and ethylene chlorohydrin. We have prepared this ester in the pure state by the action of silicon tetrachloride on a benzene solution of ethylene chlorohydrin, and have further employed the modified method for the preparation of *tetra-2 : 2′-dichloroisopropyl orthosilicate* $Si[O{\cdot}CH(CH_2Cl)_2]_4$. These substituted alkyl orthosilicates are faintly sharp smelling, highly viscous liquids. Measurements of the parachor of these liquids show that the parachor constant of silicon in them is much higher than in the simpler compounds of this element. The change in the value of the constant with increasing molecular weight M and complexity of the compound is evident from Table I.

TABLE I.

Parachor constant of silicon.

	M.	[*P*].		*M*.	[*P*].
Silicon tetrachloride	169·9	25·0	Tetra-*n*-propylsilicane	200·4	30·9
Methyl orthosilicate	152·2	26·3	Tetraphenylsilicane	336·5	37·3
Ethyl orthosilicate	208·3	26·8	Tetra-2-chloroethyl orthosilicate	346·1	38·7
Tetraethylsilicane	144·3	31·6	Tetra-2 : 2′-dichloro*iso*propyl orthosilicate	540·0	32·6

Halogenoalkyl orthophosphates have been prepared by a variety of methods. Plimmer and Burch (*J.*, 1929, 284) obtained 3 c.c. of tri-2-chloroethyl orthophosphate, $PO(O{\cdot}CH_2{\cdot}CH_2Cl)_3$, by direct interaction of phosphorus oxychloride and ethylene chlorohydrin. The substance is reported to have b. p. 140°/40 mm. and d 1·39. We have prepared the compound in quantity by the controlled interaction of a benzene solution of phosphorus oxychloride and a pyridine–benzene solution of ethylene chlorohydrin. The compound so obtained is a colourless, fairly viscous liquid, b. p. 180°/5 mm., $d_4^{20°}$ 1·4256, and analysis in conjunction with parachor measurements proved that the substance has the structure $O{\leftarrow}P(OCH_2{\cdot}CH_2Cl)_3$. *Tri-2 : 2′-dichloroisopropyl orthophosphate*, $O{\leftarrow}P[O{\cdot}CH(CH_2Cl)_2]_3$, was also prepared by the same method from glycerol dichlorohydrin. The viscosity of this ester was so high that its surface tension could not be measured by the Jaeger–Sugden method.

EXPERIMENTAL.

The substances and solvents used in the preparative work had all been carefully purified, and the liquids were redistilled with exclusion of moisture immediately before use.

Tri-2-chloroethyl Orthoborate.—The apparatus consisted of a 500-c.c. round-bottomed flask connected to a Soxhlet extractor, which was provided with a thermometer in the vapour space and with a reflux condenser. Boric anhydride (17·4 g.) and ethylene chlorohydrin (200 c.c.) were placed in the flask, and the Soxhlet thimble was charged with anhydrous copper sulphate (70—80 g.). A small cone of filter-paper, apex downward, was placed at the top of the thimble in order to direct the liquid condensate, falling from the condenser and the thermometer, to the centre of the copper sulphate, and thus ensure optimum conditions for the removal of water. The mixture in the flask was refluxed in an oil-bath kept at 170—180° for 2 hours during which period the temperature of the vapour in the Soxhlet enclosure rose to 120°. At this stage the thimble was replaced by another containing a similar quantity of anhydrous copper sulphate. The contents of the first thimble were filtered at the pump and the filtrate returned to the reaction vessel. The mixture was refluxed for a further 2—3 hours while the bath temperature was slowly raised to 200°.

The reaction mixture was transferred to a distillation apparatus, and the excess of chlorohydrin removed at a pressure of 200 mm. by distillation from an oil-bath at 190°. The residue was fractionated under reduced pressure in a Claisen unit; the pure *ester* had b. p. 117°/5 mm., 133°/10 mm., 143°/15 mm., 156°/25 mm., 175°/50 mm. Yield 90%. The material was analysed for C, H, and Cl by the usual methods, and boron was estimated by adding about 0·7 g. of the ester to 30—40 c.c. of carbon dioxide-free water, then 5 g. of mannitol, and titrating the solution with 0·1N-sodium hydroxide with phenolphthalein as indicator (Found : C, 28·7; H, 4·9; Cl, 43·1; B, 4·3. $C_6H_{12}Cl_3O_3B$ requires C, 28·9; H, 4·8; Cl, 42·7; B, 4·3%). The ester is a colourless liquid and has little odour. Like the simple trialkyl orthoborates, it undergoes rapid hydrolysis in a moist atmosphere, forming boric acid and ethylene chlorohydrin.

Tri-2 : 2′-dichloroisopropyl Orthoborate.—This was prepared from boric anhydride and glycerol αα′-dichlorohydrin with toluene as a solvent. This procedure avoided the use of a large excess of the chlorohydrin and enabled the eliminated water to be removed by distillation.

The apparatus consisted of a round-bottomed flask (500 c.c.) provided with a well-lagged eight-pear column in communication with a condenser. The flask was charged with boric anhydride (7 g.), the dichlorohydrin (66 c.c.), and toluene (200 c.c.), and the mixture was heated in an oil-bath. The temperature of distillation was allowed to rise to 115° during 90 minutes. The upper layer of the distillate was then separated from the aqueous layer and returned to the reaction flask. The process was repeated until the condensate was free from water. The excess of toluene was then distilled from the reaction mixture, and the residue fractionated in a Claisen apparatus. The pure borate was collected at 198°/5 mm.; at higher pressures the liquid boiled at 215°/10 mm., 227°/15 mm., and 240°/25 mm. (Found: C, 27·0; H, 3·7; Cl, 53·8; B, 2·7. $C_9H_{15}O_3Cl_6B$ requires C, 27·3; H, 3·8; Cl, 53·9; B, 2·7%). The ester resembles the lower homologue in its properties.

Tetra-2-chloroethyl Orthosilicate.—The reaction vessel consisted of a 1-l. distillation flask with its side tube bent upwards and connected to an inclined condenser, to the upper end of which was attached a downward-directed pipette. The latter passed through a stopper in a conical flask provided with a guard tube of calcium chloride. The distillation flask was provided with a stopper carrying a dropping funnel, and a gas-inlet tube reaching to the bottom of the flask. A solution of ethylene chlorohydrin (90 c.c.) in benzene (150 c.c.) was placed in the flask, and the end of the pipette immersed in ethylene chlorohydrin (10 c.c.) in the conical flask (cooled in a freezing mixture) in order to trap silicon tetrachloride vapour. A solution of silicon tetrachloride (38 c.c.) in benzene (100 c.c.) was added dropwise to the ethylene chlorohydrin solution, which was cooled in an ice–salt mixture, so that hydrogen chloride was quietly evolved during a period of 90 minutes. The freezing bath was then replaced by a water-bath, and the mixture slowly brought to the boil during 2 hours. At this stage the contents of the trap were transferred to the reaction flask, and the mixture was gently boiled for a further 2—3 hours while a stream of dry carbon dioxide was led through the solution to remove hydrogen chloride. The solvent was removed by distillation, and the residue fractionated in the usual manner. The pure ester had b. p. 174°/5 mm., 188°/10 mm., 205°/20 mm., 227°/50 mm. At atmospheric pressure the liquid boiled at 320° with slow decomposition. Yield 88%. It is a colourless, slightly viscous liquid with a slightly sharp odour. It undergoes little hydrolysis when treated with boiling water, but the hydrolysis is rapid in boiling alkali solution.

Tetra-2 : 2′-dichloroisopropyl Orthosilicate.—This ester was prepared by refluxing a mixture of glycerol αα′-dichlorohydrin (60 c.c.), silicon tetrachloride (19 c.c.), and benzene (250 c.c.) for 8 hours in a stream of dry carbon dioxide to effect complete removal of hydrogen chloride. The solvent was removed by distillation, and the residue fractionated under reduced pressure. The pure *silicate* distilled at 244°/5 mm., 253°/10 mm., and 259°/15 mm. Yield 90% (Found: C, 26·8; H, 3·8; Cl, 51·5; Si, 5·2. $C_{12}H_{20}O_4Cl_8Si$ requires C, 26·7; H, 3·7; Cl, 52·5; Si, 5·2%). For the silicon determination a small weight of the ester was carefully treated directly with a mixture of sulphuric and fuming nitric acids in a covered crucible, then warmed, and finally ignited to silica. The freshly distilled ester is a colourless, highly viscous liquid, which, on standing for several hours, becomes pink. This is probably due to the separation of silica in highly disperse condition. The ester is insoluble in water, but is hydrolysed by boiling sodium hydroxide solution.

Tri-2-chloroethyl Orthophosphate.—The apparatus for the preparation of this substance consisted of a 1-l. flask provided with a dropping funnel, a mercury-sealed stirrer, and an exit tube fitted with a guard tube of calcium chloride. To a well-cooled, thoroughly stirred mixture of ethylene chlorohydrin (100 c.c.), pyridine (120 c.c.), and benzene (300 c.c.) was added dropwise a solution of phosphorus oxychloride (46 c.c.) in benzene (100 c.c.) during 90 minutes. Stirring was continued for a further 3 hours, and the mixture was then set aside for 24 hours. The pyridine hydrochloride was filtered off at the pump, and washed with benzene (60 c.c.). The benzene was removed from the reaction mixture by distillation, the residue washed with water, and then dried before being subjected to fractionation. The ester boiled at 180°/5 mm., 194°/10 mm., 202°/15 mm., 214°/25 mm. In view of the great discrepancy between our values and those given by Plimmer and Burch (*loc. cit.*) for the b. p. and density, our material was subjected to analysis. Chlorine was estimated by the Carius procedure. For the phosphorus determination, on the advice of Dr. D. T. Lewis, we heated a small weight of the ester with concentrated sulphuric and fuming nitric acids in a Kjeldahl flask until clear, neutralised the mixture with ammonia, then acidified it with acetic acid, and treated it in boiling solution with slight excess of uranyl acetate and ammonium acetate; the precipitate was ignited to uranyl pyrophosphate, which was weighed (Found: C, 25·2; H, 4·7; Cl, 37·5; P, 11·2. $C_6H_{12}O_4Cl_3P$ requires C, 25·1; H, 4·2; Cl, 37·3; P, 10·9%). Further confirmation of the structure of the compound is furnished by the parachor measurements described below. The *ester* is a colourless, fairly viscous liquid with a faint buttery smell. It is not appreciably hydrolysed by boiling water and only slightly by sodium hydroxide solution.

Tri-2 : 2′-dichloroisopropyl Orthophosphate.—This ester was prepared by stirring a well-cooled mixture of glycerol αα′-dichlorohydrin (60 c.c.), pyridine (48 c.c.), and benzene (150 c.c.) with a solution of phosphorus oxychloride (18 c.c.) in benzene (100 c.c.) in accordance with the previously described procedure. After separation of the pyridine hydrochloride, the benzene was distilled from the solution, and the residue was washed with sodium hydroxide solution and then dried before fractionation. The *ester* was collected at 236—237°/5 mm.; it also boiled at 246°/10 mm. and 252°/15 mm. Yield 50% (Found: C, 24·8; H, 3·7; Cl, 49·4; P, 7·6. $C_9H_{15}O_4Cl_6P$ requires C, 25·0; H, 3·5; Cl, 49·4; P, 7·3%). It is not hydrolysed by water or to any appreciable extent by sodium hydroxide solution.

All the esters described above are miscible with alcohol, ether, or benzene.

Boiling Points and Densities.—These physical constants were determined in the manner described by Evans, Davies, and Jones (*J.*, 1930, 1311); the densities, $d_{4^\circ}^{20^\circ}$, in g. per c.c., are recorded in Table II. The following equations give for each ester the b.p., t° c., under a pressure p mm. of mercury.

$B(O{\cdot}CH_2{\cdot}CH_2Cl)_3$	$\log_{10} p = 8{\cdot}4144 - 3012/(t + 273{\cdot}2)$
$B[O{\cdot}CH(CH_2Cl)_2]_3$	$\log_{10} p = 9{\cdot}2584 - 4032/(t + 273{\cdot}2)$
$Si(O{\cdot}CH_2{\cdot}CH_2Cl)_4$	$\log_{10} p = 10{\cdot}1634 - 4237/(t + 273{\cdot}2)$
$Si[O{\cdot}CH(CH_2Cl)_2]_4$	$\log_{10} p = 18{\cdot}1127 - 9009/(t + 273{\cdot}2)$
$PO(O{\cdot}CH_2{\cdot}CH_2Cl)_3$	$\log_{10} p = 10{\cdot}6449 - 4505/(t + 273{\cdot}2)$
$PO[O{\cdot}CH(CH_2Cl)_2]_3$	$\log_{10} p = 16{\cdot}5224 - 8065/(t + 273{\cdot}2)$

Refractive Indices.—These were determined as described by Jones, Davies, and Dyke (*J. Physical Chem.*, 1933, **37**, 583), and the values are recorded in Table II.

TABLE II.

Substance.	$d_{4^\circ}^{20^\circ}$.	$n_F^{20^\circ}$.	$n_D^{20^\circ}$.	$n_C^{20^\circ}$.
$B(O{\cdot}CH_2{\cdot}CH_2Cl)_3$	1·2780	1·4611	1·4556	1·4533
$B[O{\cdot}CH(CH_2Cl)_2]_3$	1·4028	1·4945	1·4883	1·4858
$Si(O{\cdot}CH_2{\cdot}CH_2Cl)_4$	1·3393	1·4699	1·4641	1·4617
$Si[O{\cdot}CH(CH_2Cl)_2]_4$	1·4538	1·5030	1·4968	1·4942
$PO(O{\cdot}CH_2{\cdot}CH_2Cl)_3$	1·4256	1·4786	1·4731	1·4708
$PO[O{\cdot}CH(CH_2Cl)_2]_3$	1·5182	1·5083	1·5022	1·4997

Viscosities.—The viscometers employed were of the Ostwald type modified to conform with the specifications of B.S.S. viscometers and the recommendations of Barr (" Monograph of Viscometry," Oxford, 1931). Owing to the wide range of viscosities exhibited by the esters, it was necessary to use three different instruments in order to obtain reasonable times of flow. Water could not be employed as calibrating liquid owing to the disparity between its viscosity and that of the esters under investigation. Accordingly, sucrose solutions (concentration 40% and 60%) were used as calibrating liquids. These solutions were prepared from " AnalaR " sucrose and were filtered through a sintered-glass filter before use. The density and viscosity values given in the International Critical Tables were used in the calculations.

The viscometers were adequately protected by means of guard tubes of calcium chloride, and the instruments were charged with a known volume of the ester under conditions which prevented the intrusion of moisture. Plugs of cotton-wool were arranged to prevent passage of dust particles into the apparatus. The measurements were carried out in a thermostat at $20° \pm 0{\cdot}02°$, and the times of flow were observed by means of a stop-watch which had been calibrated against a standard chronometer. All measurements were conducted with due observance of the customary precautions.

Surface Tensions.—These were measured by the Jaeger–Sugden method in the apparatus described by Bowden and Butler (*J.*, 1939, 83). The apparatus was calibrated in the usual way with benzene, and the esters were freshly distilled immediately before use.

The results are collected in Table III, where η is the viscosity in centipoises, γ is the surface tension in dynes per cm., and $[P]$ the parachor.

TABLE III.

Substance.	$\eta^{20°}$.	$\gamma^{20°}$.	$[P]_{obs.}$	$[P]_{calc.}$
$B(O{\cdot}CH_2{\cdot}CH_2Cl)_3$	6·871	39·19	488·5	473·3
$B[O{\cdot}CH(CH_2Cl)_2]_3$	287·1	43·40	722·6	701·9
$Si(O{\cdot}CH_2{\cdot}CH_2Cl)_4$	9·830	39·56	647·9	634·2
$Si[O{\cdot}CH(CH_2Cl)_2]_4$	579·6	42·28	946·6	940·0
$PO(O{\cdot}CH_2{\cdot}CH_2Cl)_3$	42·90	43·83	515·2	513·0
$PO[O{\cdot}CH(CH_2Cl)_2]_3$	2901	—	—	—

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179. *The Chlorination of Methyldi-2-(chloroethyl)amine and Related Compounds.*

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Chlorinations of the bases methyldi-(2-chloroethyl)amine, ethyldi-(2-chloroethyl)amine and tri-(2-chloroethyl)amine have been studied, using for this purpose (*a*) free chlorine, (*b*) *N*-chloroimides, and (*c*) aqueous bleaching powder. Each reaction leads to dealkylation, due to α-chlorination, *e.g.*:

$$Cl_2 + N(CH_2{\cdot}CH_2Cl)_2{\cdot}CH_3 \longrightarrow N(CH_2{\cdot}CH_2Cl)_2{\cdot}CH_2Cl + HCl \quad . \quad . \quad . \quad . \quad . \quad . \quad (1)$$

$$N(CH_2{\cdot}CH_2Cl)_2{\cdot}CH_2Cl + H_2O \longrightarrow HCl + CH_2O + NH(CH_2{\cdot}CH_2Cl)_2 \quad . \quad . \quad . \quad . \quad . \quad (2)$$

but β-chlorination always occurs concurrently.

Aldehydic products were characterised as 2 : 4-dinitrophenylhydrazones, whilst the secondary bases were characterised either as picrates or as *p*-nitrobenzoyl derivatives. When bleaching powder was used the secondary bases yielded, in part, oily *N*-chloroamines.

The salts of these tertiary bases are all highly resistant to chlorination.

IN view of the many similarities between the tertiary bases, $NR(CH_2{\cdot}CH_2Cl)_2$, and 2 : 2′-dichlorodiethyl sulphide, $S(CH_2{\cdot}CH_2Cl)_2$, it has been a matter of importance to compare the chemical reactions of substances of these types with chlorinating and oxidising agents. In contrast to the reactions of 2 : 2′-dichlorodiethyl sulphide, it has been found that any chlorinating agent must be used in a very large excess to effect complete reaction with a tertiary base, since the chemical changes proceed in successive stages, of which the first appears to be the most sluggish. Moreover, the reaction of an amine with chlorine yields hydrogen chloride, and unless this is neutralised immediately, there is formed an organic ammonium salt, $(R_3NH)^+Cl^-$, which is resistant to chlorination.

Nevertheless, it has been possible to trace the systematic breakdown of these tertiary bases by successive chlorination of the attached alkyl groups. *N*-Chloroimides, which will chlorinate smoothly in organic solvents without the immediate production of hydrogen chloride, have been found to be valuable reagents in effecting this diagnosis. The study of the chlorination of methyldi-(2-chloroethyl)amine has afforded the simplest results, in the light of which it has been possible to interpret the reactions of its analogues.

When methyldi-(2-chloroethyl)amine, in cold carbon tetrachloride solution, is treated with chlorine, at least half of the base is precipitated as the hydrochloride, and the solution thereafter fumes in moist air, giving off hydrogen chloride and a little formaldehyde. The filtered carbon tetrachloride solution, after treatment with water, contains both formaldehyde and glyoxal. The main initial chlorination reaction is evidently (1), since when the *N*-chloroimide of 2 : 4 : 6-trichlorobenzanilide, $NClBz{\cdot}C_6H_2Cl_3$, is used as the chlorinating agent in the same solvent 2 : 4 : 6-trichlorobenzanilide crystallises out almost quantitatively, and the filtrate, on treatment with water, gives hydrochloric acid and formaldehyde, together with the secondary base di-(2-chloroethyl)amine (reaction 2), which was characterised as its *p*-nitrobenzoyl derivative.

Simultaneously, however, there is some attack on the 2-chloroethyl group in both the 1 and the 2 position, since glyoxal, chloral, and methyl-2-chloroethylamine have all been identified as reaction products when the

N-chloroimide was used in excess (2—3 equivalents). Whilst chlorination in the 1-position leads to the production of aldehydes, the β-chlorination involves the liberation of some hydrogen chloride which, in a solvent such as carbon tetrachloride or chloroform, immediately precipitates some of the base as the inert hydrochloride.

The chlorination of ethyldi-(2-chloroethyl)amine proceeds similarly. With chlorine in carbon tetrachloride about 78% of the base is precipitated as the hydrochloride, the remainder being chlorinated, mainly at the ethyl group. When only one equivalent of *N*-chloroimide was used for chlorination, acetaldehyde could be isolated as a reaction product, but larger quantities of chlorinating agent led to the formation of glyoxal, chloral, and glyoxylic acid, together with di-(2-chloroethyl)amine. Triethylamine was shown to react in a similar manner, and much more rapidly than did the ethyldi-(2-chloroethyl)amine.

Chloroacetaldehyde could not be identified as an initial product of the reaction between *N*-chloroimides and tri-(2-chloroethyl)amine in carbon tetrachloride solution, though glyoxal and di-(2-chloroethyl)amine were regularly found. Chloroacetaldehyde was, however, characterised as a product of the reactions of free chlorine with aqueous solutions of the hydrochlorides of both methyldi-(2-chloroethyl)amine and tri-(2-chloroethyl)amine.

Since the α-chlorination products of these tertiary amines are immediately decomposed by water, with liberation of hydrochloric acid, whereas β-chlorination products (*e.g.*, dichloroacetaldehyde, chloral) are only hydrolysed slowly, it was possible to estimate the relative percentages of α- and β-chlorination effected by *N*-chloroimides. Typical results are given in the Table.

Chlorination of $N(CH_2{\cdot}CH_2Cl){\cdot}CH_3$ *with* $NClBz{\cdot}C_6H_3Cl_2$ *in Carbon Tetrachloride Solution.*

Mols. of *N*-chloroimide taken per mol. of base.	Mols. of *N*-chloroimide used per mol. of base.	Mols. of HCl formed per mol. of base.	Mols. of active Cl not converted into HCl.	α-Chlorination (%).
		(*a*) Reaction time 43 hours.		
1·028	0·995	0·427	0·568	42·9
1·028	0·993	0·430	0·563	43·3
2·054	2·044	0·834	1·190	40·8
2·054	2·043	0·854	1·189	41·8
3·083	2·734	1·116	1·618	40·8
		(*b*) Reaction time 48 hours.		
2·585	2·473	0·978	1·494	39·6
2·585	2·473	0·973	1·500	39·3
3·440	3·080	1·188	1·892	38·6
3·440	3·100	1·277	1·873	39·6

Chlorination of $N(CH_2{\cdot}CH_2Cl)_3$ *with* $NClBz{\cdot}C_6H_2Cl_3$ *in Carbon Tetrachloride Solution.*

0·931	0·903	0·293	0·611	32·4
1·863	1·806	0·624	1·184	34·5
2·794	2·555	0·875	1·680	34·2
3·725	2·474	0·889	1·585	35·9

These figures are sufficiently consistent and reproducible to indicate that the α- and the β-chlorination processes must occur as simultaneous reactions, for even when excess of the chlorinating agent was used the percentage of α-chlorinated product remained substantially constant. It will be noted that β-chlorination appears to occur slightly more easily than α-chlorination.

The action of aqueous calcium hypochlorite on these tertiary bases is similar to, but somewhat more complicated than, that of anhydrous chlorinating agents. When methyldi-(2-chloroethyl)amine is added to a freshly filtered solution of bleaching powder a vigorous reaction occurs and the mixture becomes hot. Calcium carbonate and calcium oxalate are both precipitated, but though the active chlorine soon disappears from the aqueous layer a noticeable amount of insoluble oil remains in the reaction mixture, unless a very large excess (over 10 mol. equivalents) of hypochlorite is used. This insoluble oil contains, besides unchanged base which can be washed out with cold dilute acid, an insoluble *N*-chloroamine, which liberates iodine from potassium iodide, and decomposes violently when heated. Analysis indicated that it is chiefly *N*-chlorodi-(2-chloroethyl)amine, $NCl(CH_2{\cdot}CH_2Cl)_2$, a sample of which was prepared for comparison from di-(2-chloroethyl)amine.

Similar *N*-chloroamines were obtained from ethyldi-(2-chloroethyl)amine and tri-(2-chloroethyl)amine. On warming with dilute hydrochloric acid they decomposed, liberating chlorine, and yielding di-(2-chloroethyl)-amine, which was identified as its *p*-nitrobenzoyl derivative. Triethylamine also gave an oil which, with acid, decomposed to diethylamine.

The aqueous filtrates from the above reactions of methyldi-(2-chloroethyl)amine invariably yielded both formaldehyde and glyoxal. When only one equivalent of hypochlorite had been used chloroacetaldehyde was also identified, together with the dimer of the original base, and also its chlorohydrin. Ethyldi-(2-chloroethyl)amine similarly yielded acetaldehyde, glyoxal, glycollic acid, and the dimer of the original base, whilst tri-(2-chloroethyl)amine gave glyoxal and chloral. From triethylamine the water-soluble reaction products were acetaldehyde, glycollic acid, and a little glyoxal; acetate could not be characterised.

It is thus evident that the action of aqueous hypochlorites on these tertiary bases is very similar to their

actions with free chlorine and subsequent hydrolysis, except that following the dealkylation there occurs a reaction between the secondary base and hypochlorite to form an *N*-chloroamine which, being non-basic and insoluble in water, is resistant to further decomposition.

$$HOCl + NHR_2 \longrightarrow NClR_2 + H_2O$$

Meisenheimer (*Ber.*, 1913, **46**, 1148) has drawn similar conclusions from his studies of the reactions of trimethylamine and triethylamine with hypochlorites, and has stressed the point that the hypochlorite evidently attacks the alkyl group and does not form the amine oxide.

Experimental.

The Reaction of Methyldi-(2-chloroethyl)amine with Chlorine.—(*a*) The base (19·5 g.) in carbon tetrachloride (250 c.c.) was treated, with cooling, with a solution of chlorine (8·86 g.; 1 mol. equiv.) in carbon tetrachloride (100 c.c.). An immediate vigorous reaction took place, and solid separated rapidly, but after being left overnight the mixture still contained some free chlorine. The solid was then filtered off, washed, and dried (17·5 g.). It was identified as the hydrochloride of methyldi-(2-chloroethyl)amine by conversion into its picrate, m. p. and mixed m. p. 134° (from methanol). Free chlorine was removed from the filtrate by aspiration, and the carbon tetrachloride was then extracted with dilute hydrochloric acid. On concentration, under reduced pressure, the extract yielded a brown gum, but the acid distillate gave a precipitate on treatment with 2 : 4-dinitrophenylhydrazine in methanol–sulphuric acid. By extraction with alcohol this precipitate was separated into alcohol-soluble formaldehyde 2 : 4-dinitrophenylhydrazone, m. p. and mixed m. p. 166°, and the insoluble orange bis-2 : 4-dinitrophenylhydrazone of glyoxal, which crystallised from *o*-dichlorobenzene in red needles, m. p. and mixed m. p. 323° (Found: C, 40·3; H, 2·83. Calc. for $C_{14}H_{10}O_8N_8$: C, 40·2; H, 2·4%). When only 0·75 equivalent of chlorine was used, formaldehyde was again detected, but not glyoxal.

(*b*) The hydrochloride of methyldi-(2-chloroethyl)amine (7·7 g.) dissolved in water (100 c.c.) was added to an ice-cold solution of chlorine (2·83 g.; 1 equiv.) in water (400 c.c.). After an hour the mixture became turbid. After 3 days the product, which still contained free chlorine, was concentrated, leaving a residue containing 5 g. of unchanged base hydrochloride, and giving a distillate which contained formaldehyde, identified as its dimedone derivative, m. p. 191°, and chloroacetaldehyde, identified as its 2 : 4-dinitrophenylhydrazone, m. p. and mixed m. p. 155°.

The reaction of ethyldi-(2-chloroethyl)amine with chlorine in carbon tetrachloride proceeded similarly; 78% of the base was precipitated as the hydrochloride. The mixture of 2 : 4-dinitrophenylhydrazones was separated, by alcohol extraction, into the alcohol-soluble 2 : 4-*dinitrophenylhydrazone* of ethyl glyoxylate, m. p. 124° (Found: 42·4; H, 3·8; N, 19·6. $C_{10}H_{10}O_8N_4$ requires C, 42·5; H, 3·6; N, 19·8%), and the alcohol-insoluble *bis*-2 : 4-*dinitrophenylhydrazone* of chloroglyoxal, m. p. 289° (Found: C, 37·3; H, 2·24; N, 24·9. $C_{14}H_8O_8N_8Cl$ requires C, 37·1; H, 2·0; N, 24·8%). These two products were shown to be formed together from chloral and 2 : 4-dinitrophenylhydrazine by condensation under the conditions used (sulphuric acid in ethyl alcohol). Reaction in the cold was shown to yield the 2 : 4-dinitrophenylhydrazone of glyoxylic acid, m. p. 194° (from dilute acetic acid); reaction in hot ethyl alcohol–sulphuric acid yielded its ethyl ester (above); whilst reaction in hot methyl alcohol–sulphuric acid yielded the *methyl* ester, m. p. 146° (Found: C, 40·4; H, 3·17; N, 21·2. $C_9H_8O_8N_4$ requires C, 40·3; H, 3·0; N, 20·9%). Reaction between chloral hydrate and 2 : 4-dinitrophenylhydrazine in hydrochloric acid yielded chloroglyoxal bis-2 : 4-dinitrophenylhydrazone (above) and *chloral* 2 : 4-*dinitrophenylhydrazone*, m. p. 152—153° (from acetic acid) (Found: C, 29·6; H, 1·72; N, 17·1; Cl, 31·8. $C_8H_5O_4N_4Cl_3$ requires C, 29·3; H, 1·54; N, 17·1; Cl, 32·5%).

The Reaction between Tri-(2-chloroethyl)amine Hydrochloride and Aqueous Chlorine.—The hydrochloride (10 g.) was dissolved in water (400 c.c.), and the solution was saturated with chlorine. An oil gradually separated. After 6 days this was decanted, and the aqueous solution was distilled under reduced pressure. The distillate yielded the 2 : 4-dinitrophenylhydrazone of chloroacetaldehyde, m. p. 155°, but no glyoxal or chloral derivatives. The residual oil dissolved, with evolution of chlorine, when boiled with dilute hydrochloric acid, and the resulting solution contained di-(2-chloroethyl)amine, which was characterised as its *p*-nitrobenzoyl derivative, m. p. 98° (see below).

The Reaction between Methyldi-(2-chloroethyl)amine and N-*Chloro*-2 : 4 : 6-*trichlorobenzanilide.*—The base (30·8 g.) was added to the *N*-chloroimide (66·5 g.; 1 mol. equiv.) in carbon tetrachloride (500 c.c.). After an induction period of a few minutes the solution became cloudy, and the temperature rose appreciably as solid was deposited. Free formaldehyde could be smelt, and when the vapours from the reaction mixture were led into a 10% alcoholic solution of dimedone its formaldehyde derivative, m. p. 191°, was precipitated. After 24 hours the pasty reaction product was filtered. The crystalline precipitate, after being washed with carbon tetrachloride and water, proved to be pure trichlorobenzanilide (59·3 g.). The aqueous washings contained the hydrochloride of the original base, and gave 21·5 g. of picrate, corresponding to 8·7 g. of unchanged base. Less hydrochloride was formed when carefully dried carbon tetrachloride was used as the solvent.

The carbon tetrachloride solution was extracted with dilute hydrochloric acid, and the extract was concentrated under reduced pressure to a viscous semi-crystalline residue; the distillate gave the 2 : 4-dinitrophenylhydrazones of both formaldehyde and glyoxal. Portions of the residue (i) on treatment with picric acid gave a picrate, from which was crystallised the picrate of unchanged methyldi-(2-chloroethyl)amine, m. p. 133°; (ii) gave a carbylamine reaction with aniline and alcoholic sodium hydroxide, and a deep blue colour, indicative of chloral, with resorcinol–potassium bromide and concentrated sulphuric acid; (iii) on treatment with *p*-nitrobenzoyl chloride and sodium bicarbonate gave a white crystalline amide, m. p. 98°, which, on heating resolidified and then remelted at about 190°. The *p-nitrobenzoyl* derivative of di-(2-chloroethyl)amine was made for comparison (Found: C, 45·7; H, 4·45. $C_{11}H_{12}O_5N_2Cl_2$ requires C, 45·4; H, 4·1%). It too had these same two m. p., as also did mixtures with the reaction product. It is probable that the resolidification may be due to dimerisation of the amide to a dipiperazinium salt.

A similar reaction was carried out between the base and excess of *N*-chloroimide. When 3 or 4 equivalents of the latter were used it was possible to isolate from the mixture of picrates [cf. (i) above] a little of the *picrate* of methyl-(2-chloroethyl)amine, m. p. and mixed m. p. 103° (Found: C, 33·4; H, 3·34. $C_9H_{11}O_7N_4Cl$ requires C, 33·3; H, 3·44%).

The *N*-chloroimide of 2 : 4-dichlorobenzanilide reacted with methyldi-(2-chloroethyl)amine in a similar manner. When 3 or more equivalents of *N*-chloroimide were used no unchanged base could be detected. The reaction was studied quantitatively (compare Table) as follows. Weighed quantities of base and *N*-chloroimide were allowed to react, in carbon tetrachloride solution, in stoppered flasks. After 48 hours, distilled water was added immediately the flasks were unstoppered; the products were transferred to a tap-funnel, the two liquid layers were separated, and the carbon tetrachloride layer was washed repeatedly with dilute nitric acid. Unchanged *N*-chloroimide was estimated iodometrically in the carbon tetrachloride layer, and ionised chloride was estimated by Volhard's method in the combined aqueous layers. Blank tests showed that the *N*-chloroimides used do not yield chloride ion by this treatment, and also that the 2-chloroethylamines used do not hydrolyse appreciably in the presence of an excess of cold dilute nitric acid. Reproducible results were obtained by using carbon tetrachloride as solvent, but not by using chloroform.

The reaction between ethyldi-(2-chloroethyl)amine and *N*-chloro-2 : 4 : 6-trichlorobenzanilide was carried out similarly. When 1 equivalent of *N*-chloroimide was used the vapours from the reaction mixture contained acetaldehyde. Other products (also identified when higher proportions of *N*-chloroimide were used) were glyoxal, chloral, and ethyl glyoxylate (as 2 : 4-dinitrophenylhydrazones) and di-(2-chloroethyl)amine (as *p*-nitrobenzoyl derivative). 4 Equivalents of *N*-chloroimide were needed to bring about the complete decomposition of the original base.

The reaction between tri-(2-chloroethyl)amine and *N*-chloro-2 : 4 : 6-trichlorobenzanilide yielded glyoxal and ethyl glyoxylate (as dinitrophenylhydrazones) and di-(2-chloroethyl)amine, isolated as the *p*-nitrobenzoyl derivative of m. p. 98° (remelts at 190°). 3 Equivalents of *N*-chloroimide effected the complete decomposition of the original base.

The reaction between triethylamine and *N*-chloro-2 : 4 : 6-trichlorobenzanilide (1 equiv. of each) in carbon tetrachloride took place immediately, with heat evolution. The reaction products were acetaldehyde and chloroglyoxal, which were identified as dinitrophenylhydrazones, and diethylamine, which was characterised as *p*-nitrobenz-diethylamide, m. p. and mixed m. p. 65—66°; 40% of the base remained unchanged. Glyoxal and diethylamine were identified as reaction products when 3 equivalents of *N*-chloroimide were used.

The Reaction between Methyldi-(2-chloroethyl)amine and Calcium Hypochlorite Solution.—Freshly distilled base (61·5 g.) was added to a freshly-filtered solution prepared from bleaching powder (100 g.) and water (450 c.c.) (2 mol. equivs. of hypochlorite by titration). After a time the mixture became hot and some insoluble calcium salts were deposited, whilst some carbon dioxide was evolved. When the solution had cooled it was found that practically all the hypochlorite had decomposed, though much oil still remained. Air was aspirated through the solution, and tests showed the presence of small quantities of both formaldehyde and glyoxal. From a similar reaction in which only one equivalent of hypochlorite was used chloroacetaldehyde was identified as its dinitrophenylhydrazone, m. p. 155°.

The solution was filtered, and the insoluble oil was extracted with light petroleum. Tests showed that the insoluble product was a mixture of calcium carbonate and calcium oxalate. The light petroleum solution was shaken with dilute acid, which removed unchanged base (identified as its picrate) and the remaining liquid was evaporated cautiously on the water-bath. There remained about 2 g. of an oil which liberated iodine from potassium iodide solution. Larger quantities of this product were obtained by controlling the initial reaction by external cooling. This oil decomposed on heating, and when kept deposited long colourless needles. It resembled *N*-chlorodi-(2-chloroethyl)amine, which was prepared for comparison by treating di-(2-chloroethyl)amine with excess of cold hypochlorite solution.

The aqueous solution from the reaction was concentrated, calcium was precipitated as the sulphate, and the picrates of the residual organic bases were fractionally crystallised. The main products were the picrates of methyldi-(2-chloroethyl)amine (m. p. 133°) and its dimer (m. p. 203—204°), the latter accounting for 50% of the original base. A trace of the picrate of the chlorohydrin of the original base was also obtained.

The reaction between ethyldi-(2-chloroethyl)amine and calcium hypochlorite solution proceeded similarly. When the vapours from the initial reaction were aspirated into 2 : 4-dinitrophenylhydrazine reagent the 2 : 4-dinitrophenylhydrazone of acetaldehyde was obtained. The light petroleum extract from the reaction with 3 equivalents of hypochlorite, after decomposition with dilute hydrochloric acid gave a mixture of bases, from which were isolated the picrates of the original base (m. p. 101°) and a *dimer* [m. p. 254° (decomp.)] (Found: C, 39·5; H, 3·85. $C_{24}H_{30}O_{14}N_6Cl_2$ requires C, 39·7; H, 4·17%). The aqueous solution was shown to contain glyoxal, and gave a strong positive test for glycollic acid when treated with chromotropic and concentrated sulphuric acids. Tests for acetate and oxalate gave negative results. From the reaction with 4 equivalents of hypochlorite there was obtained a pale yellow oil, which gave the reactions of an *N*-chloroamine. After decomposition with hydrochloric acid this oil gave a mixture of the hydrochlorides of the original base (picrate, m. p. 100°) and di-(2-chloroethyl)amine (*p*-nitrobenzoyl derivative, m. p. 98°). 8 Equivalents of hypochlorite were needed to effect the complete destruction of the original base.

Analogous reactions of tri-(2-chloroethyl)amine yielded chloral, glyoxal, and *N*-chlorodi-(2-chloroethyl)amine, whilst triethylamine gave acetaldehyde, glyoxal, glycollate, and a small amount of an *N*-chloroamine, which after decomposition with hydrochloric acid was identified, by the formation of *p*-nitrobenzdiethylamide, m. p. and mixed m. p. 64—65°, as *N*-chlorodiethylamine.

The β-chlorinated tertiary amines all inflamed when treated, in bulk, with dry bleaching powder, and this was the most rapid way of effecting their destruction.

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CHEMICAL DEFENCE RESEARCH DEPARTMENT, MINISTRY OF SUPPLY. [*Received, February 14th*, 1946.]

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180. *Side-chain Bromination of Some Alkylnaphthalenes with* N-*Bromosuccinimide.*

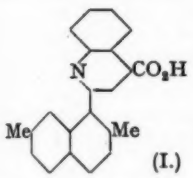
By NG.PH.BUU-HOÏ and JEAN LECOCQ.

It is shown that the reaction between *N*-bromosuccinimide and some alkylnaphthalenes results in every instance in the formation of side-chain brominated compounds. Convenient methods for the synthesis of sapotalene (1 : 2 : 7-trimethylnaphthalene) and other derivatives of 2 : 6- and 2 : 7-dimethylnaphthalene are described.

IT was found by one of us (Buu-Hoï, *Annalen*, 1944, **556**, 1) that when *N*-bromosuccinimide reacted with β-methylnaphthalene, bromination took place exclusively in the methyl group. This observation leads to a convenient method for the preparation of β-bromomethylnaphthalene, which was not hitherto readily accessible. Since those preliminary studies, a broader investigation has been made to ascertain whether this method would prove of value for the synthesis of similar unknown side-chain brominated compounds of the type $Ar{\cdot}CH_2Br$. This paper deals with the behaviour of some alkylnaphthalenes towards *N*-bromosuccinimide. α-Methylnaphthalene could be converted into α-bromomethylnaphthalene in very high yield, and this suggests that no differences in the reactivity of the methyl group exist between the two isomeric methylnaphthalenes. α-Ethylnaphthalene has been found to be far more reactive than its lower homologue, but the bromide of the α-1-bromoethylnaphthalene thus obtained was very unstable towards heat, and spontaneously decomposed in the reaction medium to give significant amounts of α-vinylnaphthalene. It is noteworthy that, in analogous

experimental conditions, acenaphthene, which is closely related to α-ethylnaphthalene, has been shown (Buu-Hoï, *loc. cit.*) to undergo nuclear substitution.

2 : 6-Dimethylnaphthalene could easily be brominated in one of the methyl groups, giving *2-methyl-6-bromomethylnaphthalene* in excellent yield. The mobility of the bromine atom in this compound is shown by its transformation into *2-methyl-6-naphthylacetonitrile*, saponification of which gave *2-methyl-6-naphthylacetic acid*.



(I.)

When a similar sequence of reactions was applied to 2 : 7-dimethylnaphthalene, the corresponding 2 : 7-*analogues* were successively obtained. For purpose of comparison, 1-bromo-2 : 7-dimethylnaphthalene has been prepared by direct treatment of 2 : 7-dimethylnaphthalene with bromine (cf. Clar and Wallenstein, *Ber.*, 1931, **64**, 2076). The Grignard compound prepared from it gave sapotalene (1 : 2 : 7-trimethylnaphthalene) on treatment with methyl sulphate, and 2 : 7-dimethyl-1-naphthol on spontaneous oxidation during its formation. Work in this field is being pursued.

The reactivity of the position 1 in the molecule of 2 : 7-dimethylnaphthalene is further shown by the results of acetylation, the sole ketone obtained being *1-acetyl-2 : 7-dimethylnaphthalene*. A cinchoninic *acid* (I) could readily be obtained by condensing the aforementioned substance with isatin in alkaline medium; but, as expected from previous observations on the influence of steric hindrance upon Pfitzinger's reactions (Buu-Hoï and Cagniant, *Bull. Soc. chim.*, 1946, **13**, 123), no cinchoninic acid could be obtained from α-naphthisatin.

Experimental.

Bromination of α-Methylnaphthalene.—A mixture of *N*-bromosuccinimide (12·5 g.), α-methylnaphthalene (10 g.), and carbon tetrachloride (65 g.) was gently refluxed on a water-bath; after 2 hours' heating, the heavy yellowish microcrystalline bromoimide had almost completely disappeared, and was replaced by white crystals of succinimide. Boiling was continued for 12 hours more, the mixture cooled in ice, and the crystals of succinimide separated by suction. The last traces of the imide were removed by shaking the filtrate with an ice-cooled dilute aqueous solution of sodium hydroxide, and then with water. The organic layer was dried (Na_2SO_4), the solvent removed, and the residue distilled in a good vacuum. α-Bromomethylnaphthalene (9 g.) was thus collected as a slightly lachrymatory yellow oil, b. p. 175/10 mm., which quickly solidified; after a single crystallisation from ligroin (b. p. 60—80°), colourless prisms, m. p. 56°, were obtained. Schmidlin and Massini (*Ber.*, 1909, **42**, 2389) described this compound as an oil; Wislicenus and Elvert (*ibid.*, 1916, **49**, 2822) and Shoesmith and Rubli (*J.*, 1927, 3098) recorded respectively m. p. 45—46° and 53°. As the direct bromination of α-methylnaphthalene requires a combined action of high temperature and irradiation with ultra-violet light, the present method is the best for preparation.

Bromination of α-Ethylnaphthalene.—The hydrocarbon used was obtained from α-acetylnaphthalene by Clemmensen reduction. α-Ethylnaphthalene (11 g.), dissolved in dry carbon tetrachloride (50 g.), was treated with *N*-bromosuccinimide (9·5 g.) under the same conditions as above. After removal of the solvent, the slightly brown oil thus obtained was strongly unsaturated towards bromine, and was vigorously shaken with a hot concentrated solution of potassium carbonate in order to decompose the last traces of brominated products. On distillation, α-vinylnaphthalene (6 g.) was isolated as an almost colourless oil, b. p. 125—135°/15 mm., which instantly decolourised a solution of bromine in carbon disulphide (cf. Brandis, *Ber.*, 1889, **22**, 2158).

Bromination of 2 : 6-Dimethylnaphthalene.—The reaction of *N*-bromosuccinimide (11 g.) with 2 : 6-dimethylnaphthalene (10 g., dissolved in 95 g. of carbon tetrachloride) was carried exactly as for α-methylnaphthalene. *2-Methyl-6-bromomethylnaphthalene* (7·5 g.) had b. p. 195—200°/14 mm., and formed silky colourless needles, m. p. 90° (decomp.), from ligroin (Found : Br, 34·2. $C_{13}H_{11}Br$ requires Br, 34·0%). These were extremely soluble in benzene and much less so in ethanol.

2-Methyl-6-naphthylacetonitrile.—A mixture of the above bromide (5 g.) and a solution of potassium cyanide (2·5 g.) in aqueous alcohol (25 c.c.) was refluxed during two hours; after dilution with water and extraction by means of ether, the organic layer was washed with water and dried (Na_2SO_4). On vacuum distillation, *2-methyl-6-naphthylacetonitrile* (4 g.) was obtained as a viscous oil, b. p. 205°/10 mm., which readily solidified on cooling, and gave silky colourless needles, m. p. 111°, after recrystallisation in alcohol (Found : N, 7·5. $C_{13}H_{11}N$ requires N, 7·7%). Saponification of this nitrile by alcoholic potassium hydroxide gave the *acid*, which separated from aqueous ethanol in glistening plates, m. p. 168° (Found : *M*, by titration, 201. $C_{13}H_{12}O_2$ requires *M*, 200). The corresponding *amide* (prepared from the viscous acid chloride by treatment with aqueous ammonia) crystallised from benzene in yellowish needles, m. p. 185° (decomp.) (Found : N, 7·4. $C_{13}H_{13}ON$ requires N, 7·0%).

Side-chain Bromination of 2 : 7-Dimethylnaphthalene.—A mixture of bromosuccinimide (11 g.), 2 : 7-dimethylnaphthalene (10 g.), and carbon tetrachloride (95 g.) was heated during 12 hours and treated as previously described. *2-Methyl-7-bromomethylnaphthalene* was obtained after two crystallisations from ligroin (b. p. 60—80°) as silky colourless needles, m. p. 100° (decomp.). This product (6 g.) had b. p. 200°/15 mm., and was strongly lachrymatory and irritating to the skin (Found : Br, 34·3. $C_{13}H_{11}Br$ requires Br, 34·0%).

2-Methyl-7-naphthylacetonitrile.—This substance was readily obtained on heating the foregoing bromide (3 g.) with potassium cyanide (2 g.) dissolved in aqueous ethanol. After distillation (b. p. 200°/10 mm.) and crystallisation from alcohol, glistening colourless prisms, m. p. 92°, were obtained (2·8 g.) (Found : N, 7·4. $C_{13}H_{11}N$ requires N, 7·7%). This *nitrile* on alkaline saponification afforded the *acid*, which crystallised from dilute alcohol in glinting plates, m. p. 166° (Found : *M*, by titration, 198. $C_{13}H_{12}O_2$ requires *M*, 200). The corresponding *amide* separated from benzene–alcohol as slightly yellowish needles, m. p. 205° (Found : N, 7·2. $C_{13}H_{13}ON$ requires N, 7·0%).

Synthesis of Sapotalene from 2 : 7-Dimethylnaphthalene.—1-Bromo-2 : 7-dimethylnaphthalene was prepared in almost theoretical yield by treating a carbon disulphide solution of 2 : 7-dimethylnaphthalene (10 g.) with bromine (10 g.) at room temperature. The product thus obtained boiled at 170°/10 mm., and melted at 52° after recrystallisation from ligroin. Clar and Wallenstein (*loc. cit.*) gave b. p. 174—180°/16 mm., m. p. 48°. The corresponding *picrate* crystallised from alcohol in bright yellow needles, m. p. 112°, extremely soluble in benzene (Found : N, 8·6. $C_{13}H_{11}Br,C_6H_3O_7N_3$ requires N, 9·0%). A solution prepared from magnesium (1·3 g.), ethyl bromide (2 g.), and 1-bromo-2 : 7-dimethylnaphthalene (13 g.) in ether (heating was prolonged to 12 hours to effect complete reaction of magnesium) was treated with excess of pure methyl sulphate, and the mixture obtained was refluxed during two hours on a water-bath. After treatment by ice-cooled dilute hydrochloric acid, the ethereal layer was shaken with 10% aqueous sodium hydroxide (fraction A), then with water, and dried (Na_2SO_4). After removal of the solvent, the remaining oil was fractionated, and yielded 2 g. of a liquid fraction, b. p. 150—155°/10 mm., which gave an orange-yellow picrate, m. p. 128°. Späth and Hromatka (*Monatsh.*, 1932, **60**, 117) recorded m. p. 129° for the picrate of sapotalene. The alkaline fraction (A) gave

on acidification with hydrochloric acid a precipitate (0·2 g.) which was extracted by means of chloroform and recrystallised from hot water. The straw-coloured silky needles of 2 : 7-dimethyl-1-naphthol thus obtained had a strong phenolic odour, melted at 95°, and gave a *picrate*, which formed red needles, m. p. 147°, from alcohol (Found : N, 10·7. $C_{12}H_{12}O,C_6H_3O_7N_3$ requires N, 10·4%).

Acetylation of 2 : 7-*Dimethylnaphthalene.*—An ice-cooled mixture of 2 : 7-dimethylnaphthalene (6 g.), acetyl chloride (3 g.), and carbon disulphide (50 c.c.) was slowly treated with finely powdered aluminium chloride (8 g.). The greenish-yellow solid thus obtained was decomposed with water and gave after standard treatment 1-*acetyl*-2 : 7-*dimethylnaphthalene* (5 g.) as a mobile, pale yellow liquid, $n^{22.5°}$ 1·6050, b. p. 190—191°/15 mm. (Found : C, 84·6; H, 7·3. $C_{14}H_{14}O$ requires C, 84·8; H, 7·0%). A mixture of this ketone (2 g.), isatin (1·4 g.), sodium hydroxide (1·1 g. dissolved in 2 c.c. of water), and ethanol (10 c.c.) was refluxed during 12 hours. After dilution with water, removal of the neutral impurities by extraction with ether, and treatment with acetic acid, 2-(2′ : 7′-*dimethyl*-1′-*naphthyl*)*cinchoninic acid* (I) was obtained (1 g.). It crystallised from acetic acid as almost colourless needles, m. p. 305° (efferv.) (Found : N, 4·5. $C_{22}H_{17}O_2N$ requires N, 4·3%). On decarboxylation, this afforded the corresponding quinoline which gave a *picrate* crystallising from nitrobenzene in microscopic yellow needles, m. p. 245—247° (Found : N, 11·2. $C_{21}H_{17}N,C_6H_3O_7N_3$ requires N, 10·9%).

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181. *The Action of Hydrogen Chloride on Isoprene.*

By W. J. Jones and H. W. T. Chorley.

Addition of hydrogen chloride to isoprene occurs in the 1 : 4-position. The purification and properties of the product are described.

Bouchardat (*Compt. rend.*, 1879, **89**, 1117), Tilden (*J.*, 1884, **45**, 410), Gadziatsky (*Bull. Soc. chim.*, 1887, **47**, 168), Aschan (*Ber.*, 1918, **51**, 1303), and Claisen, Kremers, Roth, and Tietze (*J. pr. Chem.*, 1922, **105**, 76) examined the reaction between hydrogen chloride and isoprene, but did not establish the constitution of the monohydrochloro-compound formed. In a sentence occurring in a paper describing their investigation of the structure of isoprene hydrobromide, Staudinger, Kreis, and Schilt (*Helv. Chim. Acta*, 1922, **5**, 745) stated that they had shown the compound to be dimethylallyl chloride, but they described neither the compound nor its preparation. Ostromisslenski (*J. Russ. Phys. Chem. Soc.*, 1915, **47**, 1983) proposed to estimate isoprene quantitatively by treatment with fuming aqueous hydrochloric acid, thereby forming 1 : 3-dichloro-3-methylbutane, but Bassett and Williams (*J.*, 1932, 2324) showed that, owing to unavoidable, but serious, losses during fractionation and separation of the product, this method was not quantitative.

The chief difficulty of the earlier investigators arose from their direct use of the fractionated product of pyrolysis of rubber, which, in addition to isoprene, b. p. 34°, contains 3-methylbut-1-ene, b. p. 24°, 2-methylbut-1-ene, b. p. 32°, and 2-methylbut-2-ene, b. p. 37°. In the present work, highly purified, freshly redistilled isoprene only has been used, and it has been found to combine readily with hydrogen chloride at ordinary temperature to give 1-*chloro*-3-*methylbut*-2-*ene*, as is indicated by the results of oxidation of the product both with permanganate and with ozone. The fact that the products it gives with neutral permanganate solution are acetic acid, chloroacetic acid, and carbon dioxide indicates that its double bond is medial and its chlorine atom terminal, while the formation of acetone and chloroacetaldehyde, identified as their respective oxidation products, acetic and chloroacetic acids, from its ozonide shows that its structural formula is $CMe_2{:}CH{\cdot}CH_2Cl$, and not $CHMe{:}CMe{\cdot}CH_2Cl$, which on similar treatment would yield acetaldehyde and monochloroacetone, the sole organic oxidation product of both of which would be acetic acid (Jones and Williams, *J.*, 1934, 834). The reaction between isoprene and hydrogen chloride is, therefore, similar to that between isoprene and hydrogen bromide, which gives 1-bromo-3-methylbut-2-ene (Claisen *et al.*, *loc. cit.*; Staudinger *et al.*, *loc. cit.*).

The boiling point, $t°$ c., of 1-chloro-3-methylbut-2-ene under a pressure, p mm. of mercury, is given, between 100 mm. and 780 mm., by the saturated-vapour pressure equation

$$\log_{10} p = 59{\cdot}1415 - \frac{4546{\cdot}103}{273{\cdot}1 + t} - 17{\cdot}1805 \log_{10} (273{\cdot}1 + t)$$

This equation, which is of the Kirchhoff type (*Ann. Physik*, 1858, **104**, 617), gives the value $4546{\cdot}103\boldsymbol{R}\log_e 10 - 17{\cdot}1805\,\boldsymbol{RT} = 7755$ cals. to the g.-molecular latent heat at the boiling point, $T = 273{\cdot}1° + 109°$, under atmospheric pressure, so that the value of the Despretz–Trouton function is 20·3, compared with 21·1, that indicated by the equation of Wartenberg (*Z. Elektrochem.*, 1914, **20**, 444) for a non-associated liquid of this b. p.

The gram-molecular volume of 1-chloro-3-methylbut-2-ene at 15°, corresponding to $d_4^{15°}$ 0·9380, is 111·5 c.c., agreeing fairly well with 114·8 c.c., the value given by Traube's rule (*Ber.*, 1895, **28**, 2724, 2924) for a liquid of its constitution, while its Lorenz–Lorentz refractivity for D light given by $d_4^{20°}$ 0·9331 and $n_D^{20°}$ 1·4450 is 29·83, which is close to 29·69, the value calculated by means of Eisenlohr's values (*Z. physikal. Chem.*, 1911, **75**, 605) of atomic and bond refractivities for a liquid of its structure. In the present work, readings of mass, temperature, pressure, and refractive index have been corrected for all known errors.

Experimental.

Preparation and Purification of Product.—The isoprene used had been prepared and purified through its sulphone by the method of Bassett and Williams (*loc. cit.*; Jones and Williams, *loc. cit.*), and had b. p. 33·9°/760 mm. Dry hydrogen chloride was bubbled for about 6 hours through 272 g. (4 mols.) of the freshly redistilled isoprene, continuously

mechanically stirred, and contained in a tared glass bottle which had been provided with a reflux condenser fitted with a calcium chloride guard-tube and was kept in ice–salt. The reaction proceeded practically in an atmosphere of hydrogen chloride. When the bottle had gained about 146 g. in weight (4 mols. of hydrogen chloride, loss of isoprene by evaporation not being allowed for), the product was fractionally distilled essentially as described by Jones and Williams (*J.*, 1934, 833). After two redistillations the fraction of b. p. 51·5—52·5°/100 mm. amounted to about 76 g., while in addition there were collected about 110 g. of less pure monohydrochloride. The material used in the following experiments was the fraction of b. p. 51·5—52·5°/100 mm., freshly redistilled for the purpose in hand.

The first distillation of the product of treatment of isoprene with hydrogen chloride permitted of a rough estimate of the relative proportions of its constituents by the method of Young and Fortey (*J.*, 1902, **81**, 752), but carried out under 100 mm. instead of normal pressure; after allowing for losses, it was so found that the product consisted of about 360 g. of the monohydrochloride, 20 g. of 1 : 3-dichloro-3-methylbutane, and 38 g. of unconverted isoprene.

The preparation was several times repeated, with variation of the conditions, but the product obtained was always the same. In some experiments, ether containing its peroxide was added originally with the isoprene, but the presence of the oxidant made no difference to the mode of addition, which, therefore, cannot be hypersensitively influenced by oxidising agents (Kharasch, McNab, and Mayo, *J. Amer. Chem. Soc.*, 1933, **55**, 2531; Kharasch and Hinckley, *ibid.*, 1934, **56**, 1243).

Properties of Product.—1-*Chloro*-3-*methylbut*-2-*ene* (Found: C, 57·2; H, 8·7; Cl, 34·0. C_5H_9Cl requires C, 57·4; H, 8·7; Cl, 33·9%) is a colourless liquid which darkens slowly, particularly in the presence of air and in sunlight. On being kept for any considerable time at its boiling point under atmospheric pressure, it decomposes slightly, but it can be safely distilled under diminished pressure; its b. p. is 52°/100 mm., 79°/300 mm., and 109°/760 mm.; it has $d_4^{15°}$ 0·9380, $d_4^{20°}$ 0·9331, and $n_D^{20°}$ 1·4450.

Its *nitrosate* (Found: N, 14·2; Cl, 18·4. $C_5H_9O_4N_2Cl$ requires N, 14·3; Cl, 18·0%), colourless needles, m. p. 105°, from carbon disulphide, separates after ½ hour when fuming nitric acid (3·7 c.c.) is dropped on to a shaken mixture of the chloro-olefin (2·5 c.c.), glacial acetic acid (6 c.c.), and *iso*amyl nitrite (4·5 c.c.), cooled with ice–salt (Wallach, *Annalen*, 1888, **245**, 243). The *nitrosochloride* (Found: N, 8·3; Cl, 42·0. $C_5H_9ONCl_2$ requires N, 8·2; Cl, 41·7%), colourless, microscopic, square plates, m. p. 117°, from carbon disulphide, forms immediately at the surface of separation when a mixture of concentrated hydrochloric acid (3 c.c.) and glacial acetic acid (2 c.c.) is added dropwise with shaking to a solution of isoprene monohydrochloride (2·5 c.c.), glacial acetic acid (5 c.c.), and *iso*amyl nitrite (2 c.c.), cooled with ice–salt (Wallach, *Annalen*, 1902, **324**, 97). Both the nitrosate and the nitrosochloride melt to bluish-green liquids, and are probably dimeric in their colourless crystalline forms (Schmidt, *Ber.*, 1903, **35**, 2336).

Oxidation by Neutral Permanganate.—To a mixture of isoprene monohydrochloride (6·9 g.) and water (80 c.c.), a small amount of hot permanganate solution was added to start the reaction, and thereafter solid potassium permanganate (50 g.) was dropped in small portions with shaking, the temperature being kept low by cooling. Some carbon dioxide was evolved, and manganese dioxide was precipitated. The oxide was reduced by passing in sulphur dioxide, and in 24 hours was completely dissolved. The pink liquid was extracted with ether, and the ethereal extract dried (Na_2SO_4). After filtration of the solution, the ether was evaporated; the residue on distillation gave 1·2 g. of b. p. 118°/760 mm., and 1·7 g. of b. p. 101—105°/20 mm.

The first fraction was proved to be acetic acid by its smell, its b. p., and by refluxing it with aniline for 3 hours, precipitating excess of aniline as sulphate, and extracting with ether; after drying, the ethereal extract on concentration gave crystals, m. p. 111°, which after recrystallisation had m. p. 113° and mixed m. p. 113·5° with pure acetanilide of m. p. 114°.

The second fraction solidified in a vacuum desiccator to a solid, m. p. 59°, which recrystallisation from ether raised to 60°, mixed m. p. 61° with pure chloroacetic acid of m. p. 62°.

Ozonolysis.—Chloroform was washed with water, left over concentrated sulphuric acid, separated, and distilled from phosphorus pentoxide, the fraction of b. p. 61° being collected. In 60 c.c. of this chloroform, 15·7 g. of isoprene monohydrochloride were dissolved, and in the course of 25 hours $1·5 \times 10^6$ c.c. of ozonised oxygen, containing 10 g. of ozone, were passed through the solution at 0°. The chloroform was then removed under reduced pressure, and the viscous, oily, ozonide treated with water and warmed to 50°. The reaction was mild, and there was no evolution of gas. The aqueous solution so obtained was oxidised with neutral permanganate in the manner described in the last section. After evaporation of the ether there was left a residue which on distillation gave 7·5 g. of b. p. 118°/760 mm. and 7·5 g. of b. p. 101—105°/20 mm.

The first fraction was identified as acetic acid by its smell, its b. p., and its formation of an anilide of m. p. 112·5°, mixed m. p. 113° with pure acetanilide. The second fraction solidified to colourless crystals, identified as chloroacetic acid by their m. p. 62°, mixed m. p. 62° with pure chloroacetic acid, and b. p. 104—105°/20 mm. The total amount of acids collected (15·0 g.) represents a 65% yield. The acetic acid is derived from the acetone, and the chloroacetic acid from the chloroacetaldehyde (Jones and Williams, *loc. cit.*, p. 831), formed in the hydrolysis of the ozonide. Formaldehyde was tested for in the aqueous decomposition product of the ozonide, but its presence could not be detected.

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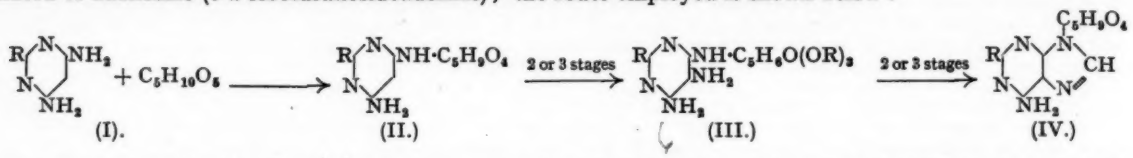
182. *Experiments on the Synthesis of Purine Nucleosides. Part XII. The Configuration at the Glycosidic Centre in Natural and Synthetic Pyrimidine and Purine Nucleosides.*

By J. DAVOLL, B. LYTHGOE, and A. R. TODD.

By a modification of Fischer and Helferich's synthesis of *d*-glucopyranosidoadenine (*Ber.*, 1914, **47**, 210) a 9-*d*-xylopyranosidoadenine has been obtained which is identical in all respects with that described in Part IX (*J.*, 1944, 652). Periodate oxidation of the following pairs of substances gives in each case a dialdehyde common to each pair. Adenosine and adenine-9-β-*d*-glucopyranoside; cytidine and cytosine-3-β-*d*-glucopyranoside; uridine and uracil-3-β-*d*-glucopyranoside. A common (almost certainly β) configuration is therefore present in the nucleosides synthesised from α-acetohalogeno-sugars, in the naturally occurring pyrimidine and purine nucleosides, and in the 9-*d*-pentopyranosidopurines synthesised by the method developed in previous papers of this series.

In previous papers of this series (Parts VI, IX, X, XI; *J.*, 1944, 318, 652, 657; 1945, 556) we have described the preparation by a general synthetic method of a number of 9-glycopyranosidoadenine derivatives closely related to adenosine (9-*d*-ribofuranosidoadenine); the route employed is shown below:



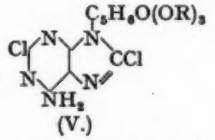
In order to apply this synthetic route to production of nucleosides of the type of adenosine it was clearly necessary to modify the first stage of the synthesis so as to allow production of a 6-amino-4-glycosidaminopyrimidine (II) possessing a furanoside structure, and experiments directed towards this end will be reported shortly. In the meantime it has been shown (Parts IX and XI, *loc. cit.*) that 6-amino-4-glycopyranosidaminopyrimidine derivatives such as (II) may, in some cases at least, be produced in both α- and β-forms. We had hoped that from these isomers the α- and β-forms of the 9-glycopyranosidoadenine derivatives (IV) would be accessible, but experiment showed that, although the αβ-isomerism is retained in a series of derivatives, *e.g.*, in the acetyl derivatives and 5-nitroso- or 5-arylazo-derivatives of (II; R = H or MeS; $C_5H_9O_4$ = *d*-xylosido), only one 5-amino-derivative (III) can be obtained from both series and consequently only one form of the 9-glycosidoadenine derivative (IV; R = H or MeS; $C_5H_9O_4$ = *d*-xylopyranosido). We therefore had to take into account the possibility that the projected synthesis of adenosine by our route might lead either to adenosine or to its αβ-isomer, and it was clearly necessary to investigate methods for determining the configuration at the glycosidic centre both in the natural nucleosides and in the synthetic 9-glycosidoadenine derivatives obtained by our route. Such a determination is also of great importance for other reasons. The stereochemical configuration of the natural nucleosides must be a factor in determining the attachment of, *e.g.*, the adenine nucleotide co-enzymes to their protein apoenzymes in enzymic dehydrogenation and transphosphorylation systems, and in the mode of union of polynucleotide and protein components in the self-duplicating nucleoprotein systems such as the plant viruses.

In the present paper we present the first experimental evidence bearing on this subject so far obtained, former information having been confined to speculation. Levene and Bass ("The Nucleic Acids," 1932, p. 136) state that it is probable that all known purine nucleosides are of the same form in view of the fact that they are all hydrolysed by the same enzyme, and Bredereck ("Fortschritte der Chemie Organischer Naturstoffe," 1938, **1**, p. 131) expresses the opinion that since almost all naturally occurring glycosides belong to the β-series the indications are that a β-glycosidic link is present in the nucleosides. Fischer and Helferich (*Ber.*, 1914, **47**, 210) mentioned their intention of examining the behaviour towards emulsin and similar enzymes of the *N*-glucosides of theophylline and adenine which they prepared by use of acetobromoglucose, but so far as we are aware the results of such experiments have not been published, nor is there in the literature any clear evidence that *N*-glycosidases exhibit the αβ-specificity and insensitivity to the nature of the aglycone which has made carbohydrases of value in configurational studies in the *O*-glycoside series.

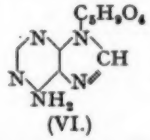
In so far as the αβ-configurations of *N*-glycosides are known at all they have been determined by one of two methods. Some *N*-glycosides show mutarotation, the direction of which can be taken as indicative of the form present. Thus Kuhn and Dansi (*Ber.*, 1936, **69**, 1745) found that the *p*-toluidineglucoside obtained by interaction of glucose and *p*-toluidine in alcohol had $[\alpha]_D^{16}$ − 92·5° ⟶ − 35·5° (*c* = 1 in alcohol), from which they concluded that it belongs to the β-series. However, even with secondary glycosides of the type NHR-sugar, mutarotation does not always occur, *e.g.*, it is absent in the *o*-nitroanilineglycosides (Kuhn and Ströbele, *Ber.*, 1937, **70**, 773) and for glycosides of the type NR_1R_2-sugar it is confined to members containing a strongly basic glycosidic nitrogen atom, *e.g.*, piperidine-*d*-glucoside (Kuhn and Birkofer, *Ber.*, 1938, **71**, 1535). The natural nucleosides and those synthetic nucleosides in which the sugar is attached to one of the nitrogen atoms of a pyrimidine or iminazole nucleus do not exhibit mutarotation, so that no information concerning their αβ-configurations can be gained in this way. The second way in which information has in the past been gained for certain *N*-glycosides seemed more suitable for our purpose. Many *N*-glycosides can be obtained by interaction of a nitrogenous base or one of its metal derivatives with α-acetobromoglucose; by making the reasonable assumption that Walden inversion takes place in such reactions, a β-configuration is deducible for the reaction product. For example, Kuhn and Dansi (*loc. cit.*) found that interaction of α-acetobromoglucose and *p*-toluidine gave a tetra-acetylglucosido-*p*-toluidine identical with that obtained by the acetylation of the *p*-toluidineglucoside mentioned above; both methods of formation lead to formulation of the product as a β-glucoside. On these grounds the theophylline- and adenine-9-*d*-glucosides prepared by Fischer and Helferich, and shown by spectroscopic evidence to possess the structures here assigned (Gulland and co-workers, *J.*, 1934, 1639; 1938, 692), are generally considered to belong to the β-series.

Although a wide variety of theophylline-7-glycopyranosides have been obtained by extension of Fischer and Helferich's procedure, the glucoside mentioned above is the only representative of the adenine-9-glycosides which has been prepared by their method. This is doubtless due in large measure to the fact that the preparation by the method of Fischer (*Ber.*, 1897, **30**, 2220, 2226) of the 2 : 8-dichloroadenine required for these experiments is tedious and impracticable if more than very small amounts are required. The modified procedure described in this paper makes the compound readily accessible; the essential features of the modified

process are employment of purified potassium urate and the use of phosphoryl chloride–dimethylaniline in the preparation of trichloropurine. By using an α-acetohalogenoxylopyranose in place of acetobromoglucose clearly a 9-*d*-xylopyranosidoadenine should be obtained which would be identical or αβ-isomeric with the compound obtained by our own method of synthesis (Part IX, *loc. cit.*). To decide which of these two alternatives is true 2 : 8-dichloroadenine was brought into reaction with α-acetochloroxylose giving in good yield a 2 : 8-*dichloro*-9-*triacetyl*-d-*xylopyranosidoadenine* (V; R = Ac), deacetylated readily to (V; R = H).



(V.)

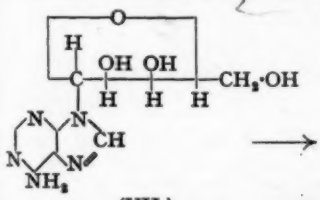


(VI.)

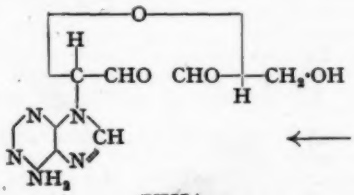
The latter could not be reduced by hydrogen iodide and phosphonium iodide, presumably because the xyloside is more labile to acid hydrolysis than the corresponding glucoside, but when (V; R = OAc) was refluxed in alcohol with Raney nickel containing adsorbed hydrogen (Mozingo, *J. Amer. Chem. Soc.*, 1943, **65**, 1013) it underwent reduction to give a mixture of a monochloro-compound, in all probability 2-*chloro*-9-*triacetyl*-d-*xylopyranosidoadenine*, and 9-*triacetyl*-d-*xylopyranosidoadenine*. Although in these first experiments the yields in this reaction were not very good, owing largely to difficulties in desorbing the reaction product from the catalyst, the method may prove valuable for the dehalogenation of more sensitive glycosides obtained by the Fischer–Helferich procedure. The possibility of isolating the 2-monochloroadenineglycosides by this method may also be of value in offering an approach to the analogues of guanosine; these different aspects are under investigation. The 9-triacetyl-*d*-xylopyranosidoadenine obtained in this way proved to be identical with a sample prepared by reductive removal of the methylthio group from 9-triacetyl-*d*-xylopyranosido-2-methylthioadenine described in Part XI (*loc. cit.*), and yielded on deacetylation with methanolic ammonia a 9-*d*-xylopyranosidoadenine identical with that described in Part IX (*loc. cit.*). The latter is therefore in all probability a β-xyloside. Preliminary evidence has already been described in Parts IX and XI (*locc. cit.*) showing that the adenine-9-*d*-ribopyranoside and 2-methylthioadenine-9-*d*-xylopyranoside belong to the same stereochemical series as (VI), so that our synthetic route apparently gives rise to β-isomerides in all cases so far investigated.

In order to apply the above method directly to determination of the configuration of adenosine, a synthesis of this nucleoside or of its αβ-isomer by the method of Fischer and Helferich would be necessary. No method of preparing the triacylhalogenoribofuranose of known configuration which would be required for this purpose has so far been described, so that an indirect method of establishing the configuration of adenosine was sought.

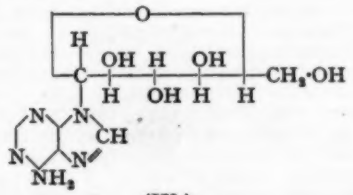
In Part VIII (*J.*, 1944, 592) we reported that purine glycosides in which the sugar residue is attached to one of the nitrogen atoms of the iminazole ring are oxidised quantitatively with sodium metaperiodate to give dialdehydes which are heterocyclic *N*-analogues of the diglycollic dialdehydes obtained by Jackson and Hudson (*J. Amer. Chem. Soc.*, 1937, **59**, 994) in their experiments with the simpler *O*-methylglycosides; we have already applied this method to determining the lactol ring structures of our synthetic purine-9-glycosides (Parts VI, IX, X, XI, *loc. cit.*) and in establishing the structure of A.T.P. as an adenosine-5′-triphosphate (Lythgoe and Todd, *Nature*, 1945, **155**, 695). As envisaged in Part VIII (*loc. cit.*) this method has proved applicable to the task of relating the configuration at the glycosidic centre in adenosine to that present in the adenine-9-*d*-glucoside of Fischer and Helferich. Oxidation of adenosine (VII) with sodium metaperiodate requires 1 mol. of oxidant, and from the reaction solution a dialdehyde can be isolated in good yield having the composition and reactions expected from the α-(*adenine*-9)-α′-*hydroxymethyldiglycollic dialdehyde* (VIII) and yielding adenine on hydrolysis with mineral acid.



(VII.)



(VIII.)

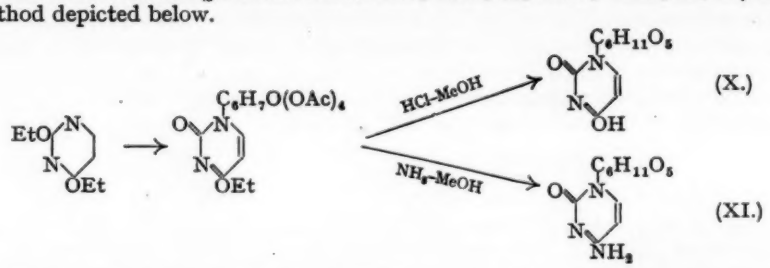


(IX.)

Similar oxidation of adenine-9-β-*d*-glucopyranoside (IX) consumes two mols. of oxidant and liberates 1 mol. of formic acid, giving a dialdehyde identical in composition and properties with that obtained from adenosine. Neither the dialdehyde (VIII) nor its picrate (obtained from oxidation of both adenosine picrate or adenine-9-*d*-glucoside picrate) shows characteristic melting point behaviour, but a comparison of their optical rotations under different pH conditions leaves little doubt of their identity. From this it follows that the configurations at C_1 are identical in adenine-9-*d*-glucoside and in adenosine; the latter is therefore properly described as adenine-9-β-*d*-ribofuranoside.

By similar means we have established that uridine and cytidine are respectively uracil- and cytosine-3-β-*d*-ribofuranosides. As reference compounds we employed the uracil- and cytosine-3-β-*d*-glucopyranosides

prepared by Hilbert and co-workers (*J. Amer. Chem. Soc.*, 1930, **52**, 4489; 1936, **58**, 60) from α-acetobromoglucose by the method depicted below.



Oxidation of the natural nucleosides involves uptake of 1 mol. of oxidant and no formic acid is liberated; the synthetic glucosides each require 2 mols. of oxidant and liberate 1 mol. of formic acid. From oxidation of cytidine (as the picrate) we isolated in good yield a crystalline *picrate* of α-(*cytosine*-3)-α′-*hydroxymethyldiglycollic dialdehyde*, which had a characteristic decomposition point; a compound of identical composition, decomposition point, optical rotation, and general properties was isolated from oxidative fission of the picrate of cytosine-3-β-*d*-glucopyranoside. From uridine and uracil-3-β-*d*-glucopyranoside we were unable to isolate the crystalline dialdehyde, but we regard the identity of the optical rotations of the two samples as sufficient proof of identity. These identities show that the natural ribofuranosides have the same configuration at the glycosidic centre as that present in the glucopyranosides obtained from α-acetobromoglucose, *i.e.*, they belong to the β-series. The above experiments also constitute proof that the glucose residue in the synthetic compounds is located at N_3, a location assigned hitherto only on the analogy of their mode of formation with that of 3-methyluracil, and on the resistance of the glucosides to hydrolysis by acids.

We are aware that the β-configurations assigned above are not completely rigid as determinations of *absolute* configuration owing to a small degree of uncertainty attaching to the assumption made at the outset, namely, that Walden inversion occurs on reaction of the acetohalogeno-sugar with the base. However, in such closely related compounds as are here considered it is most unlikely that inversion takes place in one case and not in another and we consider that a high degree of certainty attaches to the assignments here made when regarded as determinations of configuration *relative* to that present in the nucleosides synthesised from α-acetohalogeno sugars.

Experimental.

Preparation of Glycosides.

2 : 6-*Dichloro*-8-*hydroxypurine*.—Since the preparation of this substance by the method described by Fischer and Ach (*Ber.*, 1897, **30**, 2208) was found unsatisfactory the following details may prove useful. A filtered solution of potassium urate (51 g. of uric acid in 4 l. of water containing 55 g. of potassium hydroxide) was allowed to cool from 60° to 20° whilst a vigorous current of carbon dioxide was passed, and the precipitated product was freed from alkali by resuspension in cold water saturated with carbon dioxide and washing on the filter with the same medium. After being washed with acetone and dried to constant weight in an air-oven at 110° the product (52 g.) was readily reduced to a fine powder (suitable for use in the next operation). The dry acid potassium urate (16 g.) contained in a Carius tube was mixed thoroughly with redistilled phosphoryl chloride (32 c.c.), and the tube, after being sealed, was heated at 185° for 19 hours. The combined contents of two such tubes were decomposed with cold water and the product was collected and purified by treatment with hot concentrated nitric acid and conversion into the ammonium salt as described by Fischer and Ach. (Yield of pure crystalline ammonium 2 : 6-dichloro-8-hydroxypurine, 9 g.)

2 : 6 : 8-*Trichloropurine*.—The following method is more convenient than the original procedure of Fischer (*Ber.*, 1897, **30**, 2220) and gives better yields. To the above dry ammonium salt (16 g.) covered with redistilled dimethylaniline (32 c.c.) redistilled phosphoryl chloride (380 c.c.) was added and the mixture heated under reflux with exclusion of moisture for 4½ hours, after which excess reagents were removed under reduced pressure, finally at 100°. The residual pale brown gum was decomposed with ice-water (350 c.c. added in one portion) and the mixture kept cold and shaken for some time; some crystalline material separated, together with a dense oil. After addition of more ice the solution was first made strongly alkaline by shaking with sodium hydroxide and then extracted with ether (2 × 350 c.c.). The separated aqueous layer, made strongly acid with hydrochloric acid, was kept for a few hours at 0° and the crude product collected and purified by conversion into the ammonium salt as described by Fischer. (Yield of pure anhydrous ammonium 2 : 6 : 8-trichloropurine, 14·5 g.) This material is suitable for conversion into 2 : 8-dichloroadenine as described by Fischer (*Ber.*, 1897, **30**, 2239).

2 : 8-*Dichloro*-9-*triacetyl*-d-*xylopyranosidoadenine*.—2 : 8-Dichloroadenine silver (10·4 g.) was ground into a thin paste with a little sulphur-free xylene, more xylene (280 c.c.) added, and one-half of the xylene distilled off so as to remove all traces of water. To the suspension, acetochloroxylose (9·8 g.) was added, and the mixture heated under reflux with exclusion of moisture for 4½ hours, filtered hot, and the residual silver chloride washed well with hot xylene (20 c.c.). The combined filtrates, cooled to 40°, were treated with light petroleum (280 c.c.; b. p. 40—60°) and the powdery precipitate collected, washed with more light petroleum, and dried in air. Crystallisation from glacial acetic acid gave the *triacetylxyloside* as colourless needles, united to form pellets, m. p. 228° after sintering at 223° [yield, 7—8 g.; $[\alpha]_D^{16°} = -46{\cdot}4°$ ($c = 1{\cdot}71$ in chloroform)] (Found: C, 41·9; H, 3·6; N, 15·2. $C_{16}H_{17}O_7N_5Cl_2$ requires C, 41·6; H, 3·7; N, 15·2%).

2 : 8-*Dichloro*-9-d-*xylopyranosidoadenine*.—The above triacetyl derivative (0·5 g.) dissolved in warm methanol (30 c.c.) was cooled to 0°, treated with methanolic ammonia (70 c.c., saturated at 0°), and set aside at 0° for 3 days. Removal of solvent under reduced pressure and crystallisation of the residue from water gave the *xyloside* as small needles (0·3 g.), m. p. 212° (decomp.) (Found in material dried at 140° in a vacuum: C, 35·5; H, 3·7; N, 20·4. $C_{10}H_{11}O_4N_5Cl_2$ requires C, 35·7; H, 3·3; N, 20·8%).

Dehalogenation of 2 : 8-*Dichloro*-9-*triacetyl*-d-*xylopyranosidoadenine*.—The triacetyl compound (500 mg.), calcium carbonate (250 mg.), and Raney nickel containing adsorbed hydrogen (10 g., prepared according to Mozingo, *loc. cit.*)

were heated together under reflux in alcohol (70 c.c.) for 8 hours. The suspension was cooled, treated with hydrogen sulphide, filtered, and the residue extracted thoroughly (Soxhlet) with hot 95% alcohol containing a small quantity of pyridine. The combined filtrate and extracts were evaporated under reduced pressure, and the residue was dried by evaporation with alcohol and crystallised from the same solvent. The first crop gave on recrystallisation from alcohol *2-chloro-9-triacetyl-d-xylopyranosidoadenine* (64 mg.), m. p. 217°, $[\alpha]_D^{14°} = -8{\cdot}0°$ ($c = 0{\cdot}67$ in chloroform) (Found: C, 45·5; H, 4·2; N, 16·1. $C_{16}H_{18}O_7N_5Cl$ requires C, 45·0; H, 4·2; N, 16·3%). The second crop recrystallised from alcohol gave *9-triacetyl-d-xylopyranosidoadenine* (35 mg.) as needles, m. p. 227°, $[\alpha]_D^{14°} = -34{\cdot}8 \pm 2°$ ($c = 0{\cdot}61$ in chloroform) (Found: C, 49·2; H, 4·8; N, 17·9. $C_{16}H_{19}O_7N_5$ requires C, 48·9; H, 4·8; N, 17·8%). By desulphurisation of 9-triacetyl-*d*-xylopyranosido-2-methylthioadenine (150 mg.) as described in Part XI (*loc. cit.*) a triacetyl compound was obtained (yield, 37 mg.) having $[\alpha]_D^{13°} = -31{\cdot}6 \pm 2°$ ($c = 0{\cdot}45$ in chloroform) and m. p. 227° alone or in admixture with the triacetyl compound described above (Found: N, 18·0. Calc. for $C_{16}H_{19}O_7N_5$: N, 17·8%).

9-d-*Xylopyranosidoadenine*.—9-Triacetyl-*d*-xylopyranosidoadenine (70 mg.; obtained by dehalogenation of the 2 : 8-dichloro derivative as described above), dissolved in methanolic ammonia (25 c.c., saturated at 0°), was set aside at 0° for 3 days, evaporated to dryness under reduced pressure, and the residue crystallised from hot water. 9-*d*-Xylopyranosidoadenine separated as colourless plates (20 mg.), m. p. 290° (decomp.) undepressed in admixture with authentic specimens obtained as described in Parts IX and XI (*locc. cit.*). It had $[\alpha]_D^{14°} = -24 \pm 4°$ ($c = 0{\cdot}17$ in water) (Found: N, 26·5. Calc. for $C_{10}H_{13}O_4N_5$: N, 26·2%). Treatment with picric acid gave a picrate, m. p. 223—225° (decomp.); m. p. of the picrate similarly obtained from authentic 9-*d*-xylopyranosidoadenine, 222—224° (decomp.); m. p. of mixture, 222—224° (decomp.).

9-*d-Glucopyranosidoadenine*.—The preparation of this glycoside has been described by Fischer and Helferich (*loc. cit.*) and by Gulland and Story (*J.*, 1938, 259), but the following observations seem worth recording. Acetobromoglucose (15·5 g.) and dry finely divided 2 : 8-dichloroadenine silver (11·4 g.), reacting together in dry xylene (145 c.c.) for 6 hours, gave 2 : 8-dichloro-9-tetra-acetyl-*d*-glucopyranosidoadenine separating as small needles from glacial acetic acid, m. p. 212—213°; the yield (10·5 g., pure) is considerably better than that obtained by Fischer and Helferich. Deacetylation and dehalogenation of the product were carried out substantially as described by those authors; we were, however, successful in obtaining the 9-*d*-glucopyranosidoadenine virtually ash-free by direct crystallisation of the crude reduction product. The pure material melted at *ca.* 207—210°, resolidified, and remelted at 275—280° (decomp.); $[\alpha]_D^{14°} = -9{\cdot}7° \pm 0{\cdot}6°$ ($c = 0{\cdot}18$ in water) (Found: C, 44·3; H, 5·2; N, 23·4; ash, 0·3. Calc. for $C_{11}H_{15}O_5N_5$: C, 44·5; H, 5·1; N, 23·5%). The mother liquors from which the above material separated gave in the usual manner the picrate, m. p. 246° (decomp.) (Found in material dried at 110° in a vacuum over phosphoric oxide: C, 37·6; H, 3·8; N, 20·9. Calc. for $C_{11}H_{15}O_5N_5,C_6H_3O_7N_3,H_2O$: C, 37·6; H, 3·7; N, 20·6%).

Synthetic Pyrimidine Nucleosides.—3-*d*-Glucopyranosidocytosine picrate was prepared according to Hilbert and Jansen (*J. Amer. Chem. Soc.*, 1936, **58**, 60) and had m. p. 214° (decomp.) (Found in material dried at 100° in a vacuum over phosphoric oxide: C, 38·6; H, 3·8; N, 16·9. Calc. for $C_{10}H_{15}O_6N_3,C_6H_3O_7N_3$: C, 38·3; H, 3·6; N, 16·7%). 3-*d*-Glucopyranosidouracil, prepared by the method of the above authors, was obtained and used as the hemihydrate, m. p. 206° (decomp.; slow heating) (Found: C, 42·5; H, 5·1; N, 10·3. Calc. for $C_{10}H_{14}O_7N_2,\frac{1}{2}H_2O$: C, 42·5; H, 5·3; N, 9·9%). After being dried in a vacuum over phosphoric oxide at 110° it had m. p. 206—208° (decomp.); $[\alpha]_D^{15°} = +22{\cdot}2°$ ($c = 1{\cdot}52$ in water).

Natural Nucleosides.—Adenosine and its picrate were prepared from an aqueous pyridine hydrolysate of yeast nucleic acid (Bredereck, Martini, and Richter, *Ber.*, 1941, **74**, 694) and isolated by the method of these authors. They were dried at 110° in a vacuum over phosphoric oxide before use. Cytidine picrate obtained from a similar hydrolysate by using the isolation procedure of Levene and Bass (" Nucleic Acids," 1931, p. 163) was obtained as the monohydrate after drying at 80° and had m. p. 183° (decomp.) (Found: C, 36·5; H, 3·7; N, 17·5. Calc. for $C_9H_{13}O_5N_3,C_6H_3O_7N_3,H_2O$: C, 36·7; H, 3·7; N, 17·1%). Uridine was isolated from the hydrolysate of yeast nucleic acid as described by Bredereck, Martini, and Richter, m. p. 164·5°, and was dried in a vacuum at 110° over phosphoric oxide.

Oxidative Fission of Glycosides with Sodium Metaperiodate.

The values of $[\alpha]_D$ given refer to the anhydrous fission products.

Fission of Adenosine.—The titrimetric investigation of this reaction has already been described (Part VIII; Lythgoe and Todd, *loc. cit.*). The product of the fission was readily isolated as follows. Adenosine (413 mg.), suspended in 0·246 M-sodium metaperiodate (10 c.c.), was set aside at room temperature for 24 hours and the *α-(adenine-9)-α'-hydroxymethyldiglycollic dialdehyde* collected, washed with water, and dried at room temperature in a vacuum over phosphoric oxide for 48 hours; it then had a composition corresponding to a dihydrate (yield, 275 mg.) (Found: C, 40·5; H, 4·9; N, 23·1. $C_{10}H_{11}O_4N_5,2H_2O$ requires C, 39·9; H, 5·0; N, 23·2%). Attempts to desolvate this material at higher temperatures or to recrystallise it from water resulted in decomposition. In the estimation of aldehyde groups by the method of Ripper (*Monatsh.*, 1900, **21**, 1079) 1 mol. of the substance combined with 0·05 mols. of potassium bisulphite. It showed no definite m. p., but gradually darkened on being heated. When dissolved in 0·1N-hydrochloric acid (25·1 mg. in 3 c.c. total volume) the solution showed a change in rotation for which at present no satisfactory explanation can be offered: $[\alpha]_D^{19°} = +36{\cdot}4°$ (initial value) $\longrightarrow -15°$ (final value after 24 hours). After hydrolysis of the dialdehyde by heating under reflux for 5 hours with concentrated hydrochloric acid, adenine was isolated from the product as the picrate, m. p. and mixed m. p. 296°. By setting aside adenosine picrate (420·7 mg.) suspended in 0·246M-sodium metaperiodate (5 c.c.) and water (5 c.c.) at room temperature for 24 hours (sodium metaperiodate used: 1·04 mols./mol. adenosine) the *picrate* of α-(adenine-9)-α'-hydroxymethyldiglycollic dialdehyde was obtained as a light yellow powder with no characteristic m. p. After being dried at 110° in a vacuum over phosphoric oxide it had the composition of a monohydrate (Found: C, 37·8; H, 3·2; N, 21·7. $C_{10}H_{11}O_4N_5,C_6H_3O_7N_3,H_2O$ requires C, 37·6; H, 3·1; N, 21·9%). The picrate had $[\alpha]_D^{14°} = -21{\cdot}2°$ ($c = 1{\cdot}4$ in 0·1N-sodium bicarbonate).

Polarimetric Investigation of the Fission.—The rotation of the dialdehyde is strongly affected by pH of the solution; the following values observed for the fission solutions are reproducible only under the conditions described. (*a*) Adenosine (252·4 mg.) dissolved in hot water (20 c.c.) and cooled to 20° was treated with 0·246M-sodium metaperiodate (5 c.c.), made up to 30 c.c. with water, and set aside at room temperature for 48 hours; titration then showed that the reaction was complete; under these conditions no separation of dialdehyde takes place. The solution had $[\alpha]_D^{20°} = -31{\cdot}7°$. (*b*) Adenosine (91·7 mg.) dissolved in hot water (7 c.c.) was cooled to 30°, treated with 0·249M-sodium metaperiodate (2 c.c.), made up to 10 c.c. with water, and set aside at room temperature for 24 hours. A portion of the fission solution (2 c.c.) was treated with 0·1465N-formic acid (0·47 c.c. ≡ 1 mol./mol. adenosine) and aqueous sodium iodate (1 c.c. containing 13·6 mg. ≡ 1 mol./mol. adenosine), these amounts being chosen to give concentrations of dialdehyde and electrolytes equivalent to those resulting in a parallel experiment using adenine glucoside. The solution had $[\alpha]_D^{14°} = -20{\cdot}7°$. (*c*) Adenosine (180 mg.), 0·75N-formic acid (0·9 c.c.), sodium iodate (133 mg.), and 0·249M-sodium metaperiodate (7·3 c.c.) were mixed (total vol., 10 c.c.) and set aside for 36 hours. A portion of the solution (2 c.c.) was then treated with 0·3N-hydrochloric acid (1 c.c.). The solution had $[\alpha]_D^{15°} = -10{\cdot}9°$ (constant during 10 hours).

Fission of Adenine 9-d-*Glucopyranoside. Titrimetric Investigation.*—Amount of glucoside used, 98·6 mg. (in a total volume of 10 c.c. containing 5 c.c. of 0·249M-sodium metaperiodate). Amount of periodate consumed after 42 hours at room temperature, 1·98 mols./mol. glucoside. Formic acid produced, 0·98 mol./mol. glucoside. The pure dialdehyde could not be isolated from fission of the glucoside, since larger concentrations of periodate had to be employed than were necessary with adenosine and the product was considerably contaminated with inorganic material. Thus when the glucoside (160 mg.), suspended in 0·249M-sodium metaperiodate (5 c.c.), was set aside for 24 hours at room temperature and then treated with aqueous sodium hydroxide (≡ 1 mol./mol. glucoside), crude dialdehyde (15 mg.) containing *ca.* 4% of ash was deposited. Dissolved in 0·1N-hydrochloric acid, this material showed a change of rotation of the same type as displayed by the dialdehyde obtained from adenosine, although initial and final values were naturally somewhat smaller owing to the presence of the inorganic contaminant. The fission product picrate was isolated as follows. The glucoside picrate (215 mg.), suspended in 0·249M-sodium metaperiodate, was set aside at room temperature for 72 hours, and the product collected, washed, and dried at 110° in a vacuum over phosphoric oxide (Found: C, 38·0; H, 3·2; N, 21·6. Calc. for $C_{10}H_{11}O_4N_5,C_6H_3O_7N_3,H_2O$: C, 37·6; H, 3·1; N, 21·9%). This material had $[\alpha]_D^{14°} = -20·7°$ ($c = 1·46$ in 0·1N-sodium bicarbonate), and showed the same behaviour on heating as did the dialdehyde picrate obtained from adenosine picrate.

Polarimetric Investigation.—(*a*) The fission solution obtained in the titrimetric investigation above had $[\alpha]_D^{14°} = -23·1°$. After addition of sodium hydroxide (≡ 1 mol./mol. formic acid produced in the fission) it had $[\alpha]_D^{14°} = -29·2°$ in fair agreement with the value recorded under (*a*) in the polarimetric investigation of adenosine. (*b*) For more accurate comparison the glucoside (18·0 mg.) suspended in 0·249M-sodium metaperiodate (0·64 c.c.) and water (up to 3 c.c. total volume) was set aside for 24 hours at 15°. The solution had $[\alpha]_D^{14°} = -21·3°$ in good agreement with the value of −20·7° obtained under identical conditions with adenosine (see (*b*) above). (*c*) Adenine glucoside (40 mg.) and 0·249M-sodium metaperiodate (2 c.c.) were mixed and set aside for 29 hours at room temperature, and 0·3N-hydrochloric acid (1 c.c.) was added. The solution had $[\alpha]_D^{14°} = -10·3°$ (constant), in agreement with the value of −10·9° obtained for the solution from adenosine as in (*c*) above.

Fission of Cytidine Picrate.—The picrate (236·5 mg., monohydrate) suspended in water (5 c.c.) and 0·2775M-sodium metaperiodate (5 c.c.) was set aside at room temperature for 48 hours (the reaction was then complete) and made up to 30 c.c. with water. Mols. oxidant used/mol. cytidine, 0·99. The yellow fission product was collected and recrystallised from water, giving the *picrate* of *α-(cytosine-3)-α′-hydroxymethyldiglycollic dialdehyde* as a crystalline powder (82 mg.) showing a fairly sharp decomposition point at 212—214° (rapid heating); $[\alpha]_D^{18°} = +57·5°$ ($c = 1·07$ in pyridine) (Found in material dried in a vacuum at 110°: C, 37·9; H, 3·2; N, 18·3. $C_9H_{11}O_5N_3,C_6H_3O_7N_3$ requires C, 38·3; H, 3·0; N, 17·9%). In the estimation of aldehyde groups by Ripper's method the substance combined with 1·80 mols. of potassium bisulphite/mol.

Fission of 3-d-*Glucopyranosidocytosine Picrate.*—Method as above. Amount of glucoside picrate used, 300·4 mg. Mols. periodate used/mol. glucoside, 2·10. Yield of dialdehyde picrate, 110 mg. (Found in material dried at 110° in a vacuum: C, 37·9; H, 3·2; N, 18·0. Calc. for $C_9H_{11}O_5N_3,C_6H_3O_7N_3$: C, 38·3; H, 3·0; N, 17·9%). In the estimation of aldehyde groups by Ripper's method the picrate combined with 1·86 mols. of potassium bisulphite/mol. It decomposed at 210—215° (rapid heating) and had $[\alpha]_D^{18°} = +56·7°$ ($c = 0·45$ in pyridine), in agreement with the properties of the dialdehyde picrate obtained from fission of cytidine picrate.

Fission of Uridine and of 3-d-*Glucopyranosidouracil.*—Amount of uridine used, 167·7 mg. Mols. of periodate consumed/mol. of uridine, 0·98. Mols. of formic acid produced/mol. of uridine, nil. Rotation of final solution (carried out using 341·4 mg. uridine in 10 c.c. total volume) $[\alpha]_D^{14°} = +16·0°$. Amount of 3-*d*-glucopyranosidouracil used, 140·3 mg. (hemihydrate). Mols. of periodate consumed/mol. of glucoside, 1·98. Mols. of formic acid produced/mol. of glucoside, 1·05. Rotation of final solution (carried out by using 149·9 mg. glucoside hemihydrate in 10 c.c. total volume), $[\alpha]_D^{18°} = +16·0°$.

We are indebted to the Department of Scientific and Industrial Research for a Maintenance Allowance held by one of us (J. D.). Grants and gifts of material from Imperial Chemical Industries Limited and from Roche Products Limited are gratefully acknowledged.

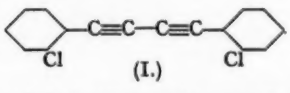
UNIVERSITY CHEMICAL LABORATORY, CAMBRIDGE. [*Received, February 28th,* 1946.]

NOTE.

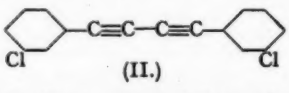
The Dipole Moments of Two Dichlorodiphenyldiacetylenes. By G. E. COATES.

THE single bonds in conjugated systems are generally shorter than those present in normal molecules; this is considered to be due to resonance effects which impart some double-bond character to the single bonds. In diphenylacetylene, for example, the "order" of the single bonds of the acetylene group is 1·48 (Robertson and Woodward, *Proc. Roy. Soc.*, 1938, *A*, **164**, 436; Penney and Kynch, *ibid.* p. 409). Partial double bonds of this type are known to impede free rotation and, conversely, the bond order appears to decrease when the molecular configuration is unfavourable to a high degree of conjugation (these effects are evident in the two forms of azobenzene discussed by Robertson, *Ann. Reports*, 1939, **36**, 175—185).

A particularly high degree of conjugation would be expected in the diphenyldiacetylene molecule, since Pauling, Springall, and Palmer (*J. Amer. Chem. Soc.*, 1939, **61**, 927) estimate that the central single bond in diacetylene has 44% double-bond character. In such highly conjugated systems the interesting possibility occurs that the degree of double-bond character present in the single bonds might be sufficient to prevent free rotation and allow *cis-trans* isomerism of suitable derivatives. The two substances 2 : 2′-dichlorodiphenyldiacetylene (I) and 3 : 3′-dichlorodiphenyldiacetylene



(I.)



(II.)

(II) have been prepared, but attempts to separate isomers have failed. It appears that the conjugation is not sufficient to prevent free rotation.

The dipole moments of (I) and (II), measured at 25° in benzene solution, are 1·92 and 1·91 D. respectively. The approximate equality of the moments indicates that the interaction between the chlorine substituent and the side chain is negligible, since any such interaction would undoubtedly affect the *ortho* much more than the *meta* compound. The

bond moments were therefore taken to be the same as in chlorobenzene, *viz.*, 1·56 D. (*Trans. Faraday Soc.*, 1934, **30**, Appendix: "A Table of Dipole Moments"). A moment of $1{\cdot}56\sqrt{2}\cos 30° = 1{\cdot}91$ D. would be expected for both compounds if there were either complete freedom of rotation or complete locking with equal amounts of *cis* and *trans* isomers. Partially restricted rotation would give other values for the moment. Since the main body of the substances melted sharply after very few crystallisations, and since no isomers could be isolated from the mother liquors, the measured moments indicate freedom of rotation.

Dipole moments were measured by means of the apparatus and procedure described by Sutton (*Proc. Roy. Soc.*, 1931, *A*, **133**, 668). Measurement of refractive indices in dilute benzene solution at 5461 A. indicated optical exaltations of 16·6 and 15·2 c.c. for the *o*- and *m*-compounds. There is undoubtedly an absorption band in the near ultra-violet, hence the electron polarisations (for the low frequency at which the dielectric constants were measured) could not be calculated from the measured refractivities; in such instances electron polarisations must be calculated from tables of atomic and bond refractivities, and extrapolated to infinite wave-length. This was the procedure adopted, since previous experience (Coates and Sutton, *J.*, 1942, 567) had shown that electron polarisations calculated from tables (Landolt–Börnstein, 5th Edition, 1923, Hauptwerk II, p. 985) agreed well with those calculated from measured refractivities. Atom polarisations were taken as 5% of the electron polarisations. Total polarisations were 154·0 and 153·1 c.c.; from the calculated orientation polarisations, 76·4 and 75·5 c.c., the moments were 1·92 and 1·91 D. respectively. Moments were not corrected for solvent effects.

2 : 2′-*Dichlorodiphenyldiacetylene*. The sparingly soluble cupric salt of *o*-chlorophenylpropiolic acid (Bergmann and Bondi, *Ber.*, 1933, **66**, 282) was prepared by the addition of a solution of the sodium salt to a slight excess of aqueous cupric chloride. The dry cupric salt (45 g.) was warmed with pyridine (150 c.c.) on a water-bath for ¾ hour; carbon dioxide was evolved. Benzene (200 c.c.) was added to the cooled and filtered solution, and the pyridine removed with hydrochloric acid. The residue from evaporation of the dried benzene solution was boiled with charcoal in ethyl alcohol and crystallised four times from ethyl alcohol; final yield of the *compound*, 8 g. of feathery crystals, m. p. 139·5—140·0° (corr.) (Found: C, 70·6; H, 3·0. $C_{16}H_8Cl_2$ requires C, 70·8; H, 3·0%). No isomer could be isolated from the mother liquors.

3 : 3′-*Dichlorodiphenyldiacetylene* was prepared by a very similar method, and was crystallised six times from ethyl alcohol and finally once from methyl alcohol; feathery crystals, m. p. 87·5—88·0° (corr.) (Found: C, 71·0; H, 3·0%). No isomer could be isolated.—The Dyson Perrins Laboratory, Oxford. [*Received, February 14th*, 1946.]

OBITUARY NOTICES.

SATYENDRANATH CHAKRAVARTI.

1903—1945.

DR. SATYENDRANATH CHAKRAVARTI was born in Calcutta in 1903. After a brilliant school and college career he took the M.Sc. degree of Lucknow University and then proceeded to Oxford in 1926 to work under (the late) Professor Willaim Henry Perkin, Jr., in the Dyson Perrins Laboratory. After taking the D.Phil. degree, he returned to India in 1929 to accept the post of Reader and Head of the Chemistry Department of the newly started Annamalai University in South India. Here he had to organise the honours and M.Sc. degree courses for the first time. Being a man of great enthusiasm, he succeeded in creating a fine department which earned a good reputation. He served as Dean of the Science Faculty and member of the Syndicate of the University; he was also elected by the members of the Syndicate to act as Vice-Chancellor of the University when there occurred a short-time vacancy. After serving the University for about seven years, Chakravarti resigned his post to the regret of all his students and colleagues and accepted the post of Chemical Examiner to the Governments of the United and Central Provinces with his headquarters at Agra. This post he held till the time of his premature death on the 28th August, 1945, in tragic circumstances.

Chakravarti is the author of forty-two original scientific publications. Through Perkin he became interested in alkaloids, and, working for his D.Phil. degree at Oxford, he successfully synthesised tetrahydroprotoberberine and some of its derivatives. Chakravarti's other work in India includes the synthesis of many more derivatives of tetrahydroprotoberberine, paraberine, ψ-opianic acid, hydrindones, homophthalic acids, and hydroxynaphthalene derivatives, and the chemical investigation of Indian medicinal plants. After his appointment as Chemical Examiner, he published papers of medico-legal and forensic interest such as methods of distinguishing various samples of opium preparations, and the detection of arsenic in burnt human bones, ashes, etc.

Chakravarti was a born teacher and commanded the admiration and respect of all his students and colleagues. He had high ideals and always tried, even at the cost of personal sacrifice, to live up to his convictions. He was greatly attached to his students. His lectures were well known for their exhaustive treatment and fine presentation and he took pains to train his students to become good chemists and not merely to pass examinations. He was a perfect gentleman and a man of sterling character.

He obtained the D.Sc. degree of Oxford University, and was elected a Fellow of the Royal Institute of Chemistry of Great Britain and Ireland, the Indian Academy of Sciences, and the National Institute of Sciences of India.

He leaves his wife and four children and a large circle of students and friends to mourn his loss.

K. GANAPATHI.

AUGUSTUS EDWARD DIXON

1860—1946

AUGUSTUS EDWARD DIXON was born on June 2nd, 1860, in Belfast.* He was the eldest son of Wakefield H. Dixon, an alderman of that city. At the Royal Belfast Academical Institute he showed early promise in scientific studies and subsequently in Trinity College, Dublin, at the age of twenty-one he obtained the Senior Moderatorship in Experimental Science with high distinction. He obtained the Gold Medal in Experimental Science and the Ekenhead Scholarship. Under the influence of Professor Emerson Reynolds he decided to make chemistry his profession but, following the usual practice of those days, he first read for a medical degree. Emerson's influence was also evident from his subsequent line of research. The greater part of Dixon's work for over thirty years was directed towards a study of the thioureas and related substances. During the qualifying stages for his medical degree he was for some time engaged as Science teacher at Clongowes Wood College, Kildare (1882—1884). He also found time for research, and in the *Proceedings of the Experimental Society of Trinity College* there are records of early papers by him, for example " The Action of Carbon on Ozone " (1882) and " A New Test for Gallic Acid " (1884); there is also a paper, " An improved Apparatus for drying Combustion Tubes," in the *Chemical News* (1888, **57**, 308).

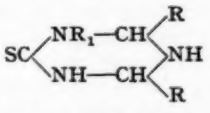
Dixon obtained the M.D. degree in 1885 and was appointed a Demonstrator in Chemistry in Trinity College for the session 1885—1886. He went to Berlin in October 1886 where he worked under Professor A. W. von Hofmann for some time. On his return to Dublin, in April 1887, he was appointed assistant Lecturer in Chemistry in Trinity College, and in October 1889 was appointed Professor of Chemistry in Queen's College, Galway. Two years later, in October 1891, he succeeded Professor Maxwell Simpson at Queen's College, Cork. The only record of this in the Council Book of University College, Cork, is that he appeared before the Council and produced Her Majesty's warrant appointing him Professor and his declaration made before a magistrate in compliance with the provisions of the Colleges Act of 1845.

* See also *Nature*, 1941, **157**, 505.

For a very long period the South of Ireland has been fortunate in having good facilities for Chemical research. At the opening of the 19th Century the Royal Academical Institute was established in Cork, and it was here that Professor Edmund Davy first discovered acetylene. In 1849, with the foundation of a Queen's College in Cork, John Blyth, M.D., was appointed first professor of chemistry and was succeeded in 1873 by Professor Maxwell Simpson, M.D. On Simpson's retirement in 1891, Dixon succeeded to the chair which he held, first in the Queen's College and later in the National University of Ireland, until his retirement thirty-three years later in 1924. He was Emeritus Professor until his death on March 3rd, 1946, in his eighty-sixth year. A period of practically one hundred and fifty years is covered by these four prominent chemists.

Dixon's output of over fifty papers deals largely with (1) reactions of *iso*thiocyanates, and (2) reactions of thiourea and its derivatives. The following abstract of these papers has been prepared by Dr. J. Wilson.

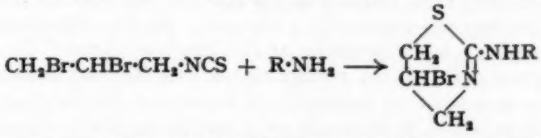
" His first publication (*J.*, 1880, **50**, 411) describes the action of acetaldehyde-ammonia and valeraldehyde-ammonia on some *iso*thiocyanates. Schiff (*Ber.*, 1876, **9**, 565) had described earlier compounds obtained by the same reaction. Dixon extended Schiff's work and assigned provisionally the following structure to the product of the reaction :



Later (*J.*, 1892, **61**, 509) Dixon examined the reaction of thiourea with aldehyde-ammonias and proved that the compounds obtained from this reaction are of the same type as those obtained from *iso*thiocyanates and aldehyde-ammonias.

" While this work was progressing he prepared a number of new substituted thioureas (*J.*, 1889, **55**, 300, 618; 1891, **59**, 561). A logical extension of this investigation was his work on the thiosemicarbazides, and he published several papers on their preparation and the phenomenon of isomerism in that series (*J.*, 1890, **57**, 257; 1892, **61**, 1012).

" Aschoff (*J. pr. Chem.* 1871, **4**, 314) had examined the action of bromine on allyl *iso*thiocyanate but failed to identify any of the products. Dixon (*J.*, 1892, **61**, 545) repeated this work and isolated dibromopropyl *iso*thiocyanate in good yield. He examined its properties and in later papers (*J.*, 1896, **69**, 17; 1901, **79**, 553) reported its reaction with several amines. The thiourea derivative was not produced but lost the elements of hydrogen bromide to give a cyclic product. He explained this reaction as follows :



" Another reaction examined carefully was that between metallic thiocyanates and acid chlorides. Miguel (*Ann. Chim. Phys.*, 1877, **11**, 289) had prepared acetyl and benzoyl thiocyanates by the interaction of the respective acid chlorides with lead thiocyanate. Though on mixing the product with aniline the substance obtained was a substituted thiourea, *e.g.*, $CH_3{\cdot}CO{\cdot}NH{\cdot}CS{\cdot}NH{\cdot}C_6H_5$ from acetyl thiocyanate and aniline, Miguel did not grasp the fact that the acyl thiocyanates show the reactions of thiocyanates and *iso*thiocyanates. Dixon re-examined this reaction, extended it to the preparation of di*iso*thiocyanates and prepared many substituted thioureas [*J.*, 1895, **67**, 565 (with Doran), 1040; 1896, **69**, 855, 1593; 1897, **71**, 617; 1899, **75**, 388]. The results (*J.*, 1901, **79**, 541) of these investigations showed conclusively that under certain conditions acyl thiocyanates sometimes exhibited the properties of thiocyanates but usually (especially with amines and alcohols) react like *iso*thiocyanates. These compounds continued to provoke his interest and in 1903 (*J.*, **83**, 84) he prepared carbonyl di*iso*thiocyanate in solution and found that it reacted with aniline to give the substituted thiourea, $CO(NH{\cdot}CS{\cdot}NH{\cdot}C_6H_5)_2$. He discovered later, with Hawthorne (*J.*, 1906, **89**, 468), that the reaction of acetyl thiocyanate with aniline at low temperature resulted in the formation of acetanilide and thiocyanic acid. At higher temperatures the acetylphenylthiourea was formed. (See also *J.*, 1906, **89**, 892.)

" An observation in 1903 (*J.*, **83**, 550) that methyl chloroformate unites spontaneously with phenylthiourea led Dixon to examine the reaction of acid chlorides on thioureas. Claus (*Ber.*, 1875, **8**, 42) had reported that a highly unstable compound was produced by adding acetyl chloride to thiourea. A re-examination of the reaction by Dixon, with Hawthorne and Taylor (*J.*, 1907, **91**, 122, 912), showed that in the case of thiourea and mono-substituted thioureas the hydrochloride of the base, $CH_3{\cdot}CO{\cdot}S{\cdot}C{<}^{NR}_{NH_2}$, was first formed which on removal of hydrogen chloride and warming rearranged and gave a di-substituted thiourea. When the α-chloro-acyl chlorides reacted with thioureas, *iso*thiohydantoins were formed (Dixon and Taylor, *J.*, 1908, **93**, 21; 1912, **101**, 558). A later communication (with Kennedy, *J.*, 1920, **117**, 74) describes the preparation of acyl *iso*thiohydantoins.

" Dixon did not confine his attention to thiourea derivatives. Manuelli and Comanducci (*Gazzetta*, 1899, **29**, 142) claimed that α-phenyl-β-*p*-tolylurea was formed by heating phenylurethane with *p*-toluidine. Dixon noted the discrepancy between the melting points reported by them for the substance and the melting point which he himself had observed in a previous experiment (*J.*, 1895, **67**, 562), and he repeated the work of these

authors. By detecting aniline in the reaction mixture he showed that the compound reported by the Italian authors was di-*p*-tolylurea. In general he found that when phenylurethane was heated with an equivalent amount of *o*- or *p*-toluidine or with naphthylamine the symmetrical di-substituted urea from the base always accompanied the mixed urea (*J.*, **1923**, **123**, 895)."

On a few occasions, Dixon, to confirm certain theories of his, had recourse to physico-chemical methods. He was an expert at mechanical operations and a first-rate glass manipulator. Further, he collaborated with Professor Hartog on the chemical aspect of certain biological problems. In these activities also he was a master of his subject. Apart from his research ability, he was an excellent and stimulating lecturer; he followed the Hofmann tradition of showing many elaborate experiments in his undergraduate classes. He also took a keen interest in the erection of new chemical laboratories in University College, Cork, and was responsible for many novel ideas in their planning and equipment. He designed with Taylor (*J.*, 1910, **97**, 374) an apparatus for demonstrating the electrolysis of hydrochloric acid solution, and with McKee (*J.*, 1923, **123**, 895) a simple apparatus for purifying mercury by air agitation with or without the usual cleansing solutions.

Dixon was of a retiring disposition and only his intimate friends were aware of his very active scientific life. He served on the Council of the Chemical Society from 1900 to 1902. He was a member in 1903 of the grants committee of the Royal Society. He became a Fellow of the Royal University of Ireland in 1908. His hobby was photography, in which he was an expert, and he was one of the founders of the Cork Photographic Society. He was President of the Society until his departure to Sidcup, Kent, on retirement in 1924.

Dixon married Miss Nina Haughton of Dublin in 1888 and his two sons graduated at University College, Cork; Wilfred (who died soon after graduation) in medicine, and Emerson in engineering. He is survived by his widow, one son, and a married daughter.

JOSEPH REILLY.

ARTHUR GEORGE GREEN.*

1864—1941.

" Life is a pure flame and we live
by an invisible fire within us."

ARTHUR GEORGE GREEN died peacefully in his sleep on September 12th, 1941, in the seventy-eighth year of his life. From leaving college in 1885 until the day of his death Green was continuously and actively engaged in the practice of chemistry. He was pre-eminently a chemist; all his enthusiasm, and it abounded in him, was for chemistry or for causes which had chemistry at the heart of them. The synthetic dyestuff industry was his foremost passion and practically all the energy of his long life was devoted to it, not merely because he had fertilised it by his early genius as an inventor, or because it furnished an outlet for his talent as an experimenter, but because he believed in it fervently as a matter of major significance in the industrial and scientific development of the nation. The dyestuff industry was a " cause " to Green. He was a servant to science, and a passionate preacher of science in industry. He was properly honoured for his work and for his devotion by his colleagues, becoming a Fellow of the Royal Society and the recipient of many honours, medals, etc., from other learned bodies. From the politician and the general public, however, Green received no recognition. On this account, and because of the intensity of his belief in the urgency of his cause, Green must have experienced many times the pangs of disappointment and frustration, but in spite of it, and of the many changes in his career, his life was happy and uninterrupted in the steady and fruitful practice of the branch of chemistry of which he was a master. To have been able to do this up to the very day of his death was his greatest reward.

Green commenced his life work in dyestuff chemistry while it was still comparatively young, both as a branch of science and as an industry. Very early in his career, he blossomed out as an inventor and ranks amongst the select band whose discoveries ensured the establishment of the great industry of synthetic organic chemicals of which the artificial colouring matters have always been the pivot and the inspiration. He suffered the chagrin of seeing the industry which had been born in this country come to its fullest fruition in another land, then in the last period of his life he saw it flourishing once more in the land of its birth.† At the end of his life Green passed his happiest days amongst the new generation of colour chemists who have arrived on the British scene with the renaissance of the industry on which he had set his heart.

Green was born a Londoner, the son of an architect, and was educated at Lancing College, Sussex. He confessed himself to have been an indifferent pupil until he was allowed to work in the almost unused chemical laboratory of the school during play hours. After matriculating, in 1880, he entered University College, London, where he studied chemistry under Williamson, physics under Oliver Lodge, and biology under Ray Lankester. At the end of his first year, he gained a gold medal and a Clothworkers' Exhibition in chemistry, and the seal was set on his career. More medals, a Tuffnell Scholarship and research work with Dr. H. F.

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† Compare the two lectures: (*a*) The Relative Progress of the Coal Tar Industry in England and Germany during the past Fifteen Years (*J. Soc. Dyers and Col.*, 1901, **17**, 285); (*b*) The Renaissance of the British Dyestuff Industry (*ibid.*, 1930, **46**, 341).

Morley followed. During college vacations Green had worked as a volunteer in the laboratory of Messrs. Williams Bros., aniline dye manufacturers of Hounslow. He introduced to the firm the " baking " process for the manufacture of sulphanilic acid, and throughout his career, with breaks from time to time, he maintained his old connexion with this ancient firm.

Green was by this time completely committed to dyestuff chemistry, and when he left College in 1885 obtained his first post as research chemist to the firm of Messrs. Brooke, Simpson & Spiller, Ltd., Atlas Works, Hackney Wick, where, incidentally, he succeeded Meldola, who was leaving to become professor of chemistry at Finsbury Technical College. While in the service of this firm Green made his first dyestuff inventions. These were of outstanding merit and included primuline, which was not only a new dyestuff but led Green to uncover an entirely new technique in the application of dyestuffs on cotton. In the light of later knowledge it is easy to see that Green's inventions at this early stage of his career could and should have built up the fortunes of a dyestuff business in this country comparable with the powerful firms which were developing in Germany. This was not to be, however, and Green, mortified at the want of appreciation of these wonderful possibilities, transferred his services in 1894 to the Clayton Aniline Company, in Manchester.

From 1894 to 1901, Green laboured at Clayton as research chemist and works manager. His earlier inventions in the primuline field were developed and greatly improved, and progress was made in other classes of dyestuffs, notably the derivatives of stilbene. Under Green's regime the Clayton works was greatly enlarged, and in addition to his many patented inventions during this period, and some publications in scientific journals, Green participated in the development of a modern modern manufacturing technique. A case in point was the establishment on a large scale of the manufacture of *p*-nitroaniline by the acetanilide route, using an aluminium reaction vessel with a silver condenser, great innovations in their day.

At the turn of the century the position of the dyestuff industry in England was critical. Green's inventions and the position he occupied augured possibilities which could be compared with what Caro, for example, had done for German industry. The manufacture of dyestuffs was already emerging from its earliest, or " rosaniline " period when Green commenced his career. In those early days it could only be reckoned as a small sundries type of industry. Now, however, owing to the progress of the azo dyes under Caro's presiding genius, and the consequent demand for intermediates on a bulk scale, a complete change had come about. The improvised technique and the elementary conceptions of plant, borrowed for the most part from other trades, which had characterised the early phase of the industry now no longer sufficed. The manufacture as well as the chemistry of dyestuffs had become scientific, and a new phase was inaugurated by the production of synthetic indigo on the large scale. The latter event saw even inorganic processes such as electrolytic alkali and chlorine, as well as contact sulphuric acid, invented and developed solely in order to meet the need of the dyestuff industry to obtain its primary products on a bigger and more economic scale. With these developments the German dyestuff firms progressed from strength to strength, a fact of which Green was keenly aware, and which caused him to despair as he came to realise his failure to arouse interest among the industrial and political leaders of this country. It is not surprising, therefore, that at this stage Green severed his connexion with industry. He left the Clayton Aniline Company in 1901.

Green's next venture was to open a private laboratory in London in order to sell his ideas and to act as a chemical consultant. Within a short time, however, he was invited to accept the chair of Colour Chemistry and Dyeing at the University of Leeds (at that time the Yorkshire College, a constituent of the Victoria University).

Green's appointment as professor, direct from industry and without any academic experience or standing, reflects considerable credit on the enterprise and judgment of those responsible at Leeds. He was, however, well fitted for the post and, although he had a most distinguished predecessor in the late Professor Hummel, Green, during the period 1903—1916, in which he occupied the chair, greatly enhanced the reputation of his department, both in teaching and in research.

Liberally endowed by the Clothworkers' Company, according to the standards of the day, Green's department at Leeds became not only an outstanding example of the teaching of applied science, but it acquired an international reputation for its research work. Graduates of universities, both in this country and abroad, came to work under Green, and the students of the department were eagerly sought after, even by the great German dyestuff firms.

The nature and the success of Green's work while in the chair at Leeds are well indicated in his original publications during this period. These are almost exclusively of a scientific character, but he never entirely lost his contact with the dyestuff industry at home and abroad, with which he had many consulting connexions. As the discoverer of a new method of dyeing Aniline Black he also had a very intimate practical contact with the dyeing trade through the grant of patent licences in many countries.

By a coincidence, one of Green's contemporaries at Leeds was Procter, head of the Department of Leather Technology. Procter too had been recruited from industry and had an international reputation, not only for the training of students in the scientific aspects of industry, but also for his pioneer work in colloid science. The importance of the teaching and the original work done by men of the type of Green and Procter in the interest of the scientific development of industry is usually insufficiently appreciated by those in authority over matters educational. The faintly acidulous attitude too often shown by the academic world towards the more " applied " aspects of advanced scientific education was not absent at Leeds; perhaps the lessons now brought

home so painfully by a technical war were not so obvious in 1914. Whatever the reasons Green was restless at the time and when war broke out was probably feeling a strong urge to get back into industry.

The war in 1914 brought new ideas and responsibilities to Green. All his forebodings and warnings about the decadence of organic chemical industry in England proved to be only too well founded when, out of our unpreparedness, we had to improvise the means to deal with a scientifically well-equipped foe. Like other academic leaders in chemistry Green was faced with the need of finding men for the understaffed factories and of assisting the Government with advice and hurriedly improvised research work. Green's experience in the dyestuffs field led him to useful contributions in many directions, for example, in the explosives field he pioneered the chlorodinitrobenzene route to picric acid (B.P. 16,607, 1915).

The dyestuff crisis was one of the most acute of the many technical problems with which the country was faced at this time. Not only was there an insufficiency of plant and experience to meet more than a small fraction of the urgent demand, but, owing to the comparative neglect of scientific research and advanced teaching in organic chemistry at the universities, there was an insufficiency of the type of men required for the hurried improvisation of an entire industry, which was what the situation called for. In this chaos Green resigned his chair at Leeds early in 1916, and took on the double responsibility of establishing the Dyestuffs Research Laboratory at the Manchester College of Technology, and at the same time acting as advisor to the firm of Levinstein, Ltd., who were at that time bearing the brunt of the increased dyestuffs production. An outstanding event of Green's connexion with this firm was his collaboration in the working out and establishment of the technical production of mustard gas on the large scale, an event which aroused much enthusiasm amongst our American allies but was attended by some academic controversy in this country (*J. Soc. Chem. Ind.*, 1919, **38**, 363r, 469r).

Green's interest did not wander from dyestuffs for very long, and the end of the war found him working whole time with Levinstein, Ltd., as director of a new research laboratory staffed very largely from the pick of the chemists released from other fields of the war effort. Green held this appointment through the troubled times which fell upon the dyestuff industry in the early years of peace. The struggling industry was the subject of much political controversy as well as many changes in management resulting from the " rationalisation " which was part of the post-war economy, on top of which it was all but ruined by the effects of the Sankey judgment.

In 1923, Green's firm, having in the meantime become the British Dyestuffs Corporation, Ltd., lost his services on account of a disagreement on policy. Green held the view that an industry dependent on scientific development should be in the hands of men having the fullest appreciation of science, that is to say, of scientists. This view was not commonly held by his contemporaries, but Green knew only too well from personal experience the disaster which the industry had suffered in this country through falling into the hands of men who lacked knowledge, and he was anxious that the mistake should not be repeated. Unfortunately he chose the wrong moment to attack, pressed his point, and lost; had he waited, he would have been successful, judging in the light of subsequent events in the industry. It is safe to say, however, that in the period during which Green directed his laboratory at Blackley the seed was sown for the great revival of the dyestuff industry which followed there later. The reason for this was the fact that wherever Green established himself his efforts were always directed along the path of originality and discovery, as the true object of research. When his old firm found itself in circumstances of greater security under the aegis of Imperial Chemical Industries, Limited, it blossomed out in an ambitious and successful research effort which commanded the respect of the world of chemical industry and secured it many commercial advantages. This success can safely be attributed to the inspiration gained in many ways, direct and indirect, from the inventive spirit of A. G. Green.

During his period at Blackley, Green's interests covered a wide field of dyestuffs invention and he revived an old attachment he had always had for the chemistry of synthetic drugs. The close connexion between drugs and dyes is well known, and it is significant that the continental dyestuff manufacturers have been responsible for the world's greatest advances in chemotherapy. It was natural, then, that Green should concern himself with this off-shoot of the dyestuff industry and in his later years his " retirement " was largely devoted to experimental work on the subject in his private laboratory. This work bore fruit in the issue on the market of sulphanilamide EOS, a useful contribution to chemotherapy, shortly after Green's death (Green and Coplans, B.P. 524,011; *idem*, *Chem. and Ind.*, 1940, **59**, 793).

Green resumed his connexion with his old colleagues in the dyestuffs industry at Blackley during the last six years of his life, when he became a consultant to Imperial Chemical Industries, Ltd., and, by his regular visits to the great laboratories which the firm had built at Blackley, was able to participate in and inspire the work of the new generation of dyestuff chemists. It was a unique opportunity for these younger men to learn from one of the early pioneers of the industry that in spite of the enormous strides which had been made on the theoretical side of chemistry in the intervening generations, and the colossal amount of publishing and patenting which had filled in the years, old Nature's lap is still full of prizes for those who will acquire the knack of putting the right kind of questions to her. To quote a Chinese proverb, " To ask well is to know much." Green was very successful in imparting the art of " asking," and his pupils have played a considerable part in the restoration of the dyestuffs industry in this country.

In personal disposition Green's character was of the mildest and gentlest. His fervent belief in science as a keynote in modern life, and in the dyestuffs industry as a keystone in modern industrial development, was

never expressed in mere pugnacity, but rather as a quest, a persistent crusade for that in which he believed with all his heart. Nevertheless there was plenty of toughness of moral fibre in Green, and through the varying phases of his career, he never once surrendered the ideals for which he had battled all his life.

Green's work earned him many honours in the worlds of science and technology. These included election to the Royal Society (1915) and the honorary degree of M.Sc. of the University of Leeds (1905). He was the recipient of the Perkin Medal in 1917. He was very proud to be made a Liveryman of the Worshipful Company of Dyers (1918) and on three occasions he was awarded the Company's Gold Medal He was an Honorary Member of the Society of Dyers and Colourists, and President in its Jubilee Year. He was elected a Fellow of the Chemical Society in 1885.

Apart from chemistry Green had few interests. He liked foreign languages and travel, and in his early days tramped and cycled extensively in continental countries. He had a happy family life and his character was seen best in this setting—a simple man whose ambition was all for his science.

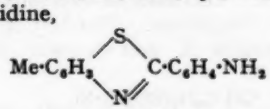
Green's domestic life was one of unclouded happiness until he lost his wife early in 1941. She was the daughter of Henry Charles Heath, a well-known miniature painter. For fifty-two years she supported him in his many struggles and vicissitudes and nursed him through several serious illnesses, for, though apparently as wiry in body as in spirit, Green's health was on the frail side. She gave him two daughters and amongst his private papers he left a most touching tribute to her brave spirit. There is no doubt that the shock of her death hastened his own end, for he followed her within a few months.

In attempting to appraise Green's life-work, one must place his merit as an inventor to the forefront. The outset of his career was signalled by a dyestuff invention which stands out in the history of that industry. Green was also a successful teacher, and, during his academic period, he turned out a great volume of original scientific papers in collaboration with the numerous research students who were attracted to his Leeds laboratory. From the beginning to the very end of his career, however, Green never ceased to give his thoughts to industrial problems and inventions.

Green's career may be divided into three periods: the early-industrial up to about 1900, the middle-academic, interrupted by the war in 1916, and the post-war industrial and consulting period. Green's war-work was an interruption which deserves special mention. Comparison of these phases is not really possible, but, in my view, the first period was the most pregnant, and it was Green's tragedy (and ours) that its potentiality was not recognised and exploited effectively for the benefit of British industry. Green " arrived " just about the end of the early, or " rosaniline " period of the dyestuffs industry. He missed, therefore, being one of that band of the earliest pioneers who in the twenty years following the discovery of mauve made fortunes and retired young.* Instead Green found employers for his young talent who were completely lacking in knowledge of the science on which the industry rested and indeed without ordinary vision, since, apparently, they thought the industry was past its hey-day, an attitude which is almost unimaginable in the light of events and is, perhaps, another example of the curious kinks in Victorian mentality.

It is a matter of history that when Green came on the scene the dyestuff industry was just entering a new phase, when its real economic possibilities were to be clearly indicated by the rise of the azo dyes and eventually confirmed by the large-scale production of synthetic indigo. This was the psychological moment for " big business " to step in. Unfortunately for this country, however, organic chemistry lay beyond the vision of its business leaders; had it been otherwise Green would undoubtedly have given the impetus in this country which men like his contemporaries René Bohn, T. Sandmeyer, and R. E. Schmidt gave on the continent, resulting in the establishment of dyestuff technology in the front rank as an industrial power-centre from which radiated eventually many other branches of organic chemical industry, *e.g.*, drugs, artificial fibres, new photographic technique, and synthetic polymers, to say nothing of the consequent developments in inorganic chemicals which the new organic industry consumed in large quantities. The fruits of Green's inventions up to about 1900 could, if properly developed, and the profits " ploughed in " to produce an ever expanding research, have established an industry in the country comparable at least with that which grew up in Germany and Switzerland. British inventiveness had proved itself in the pioneer period of the dyestuffs industry following Perkin's discoveries; it has proved itself again in the renaissance which followed after the Great War. Green's tragedy was that his talent was not exploited in his hey-day, and it took a war to prove that his views on the importance of the dyestuff industry to this country were not over-stated. In the dangerous time ahead of us we must see to it that the lessons provided by Green's career are not forgotten.

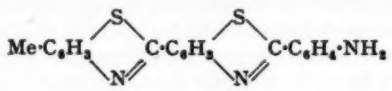
Green's earliest invention was, it so happened, his most outstanding one, the discovery of primuline in 1887 (*J. Soc. Dyers and Col.*, 1888, **4**, 39; 1917, **33**, 137; *J.*, 1889, **55**, 227). By the action of sulphur on *p*-toluidine, the thiazole, dehydrothiotoluidine,



is formed; this substance is not a dyestuff. Green, studying this reaction, discovered that a more complex

* Cronshaw," In Quest of Colour," Society of Chemical Industry Memorial Lecture (*Chem. and Ind.*, 1935, **54**, 515, 547).

base can be obtained by the use of more sulphur and a higher temperature. The new base when sulphonated gave a dyestuff having affinity for cotton, which is dyed a bright pure yellow without the aid of a mordant. The new dyestuff has been shown to consist substantially of a sulphonic acid of the base :



The derivation from *p*-toluidine is obvious; the position of the sulphonic group has not yet been proved.

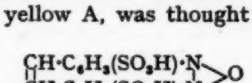
The new dyestuff, although fugitive to light, was an attractive addition to the, at that time, very limited range of direct dyeing cotton colours (Congo red, the first of the benzidine dyes, was less than three years old), but Green had still further work to do before primuline achieved the position it was later to assume as a major dye. Green applied his mind to the technique of dyeing and discovered the process of diazotising and developing on the fibre those substantive dyes which contain a reactive amino group. Primuline in this way gave a red with β-naphthol which achieved great industrial importance, and is still largely used though now past its hey-day on account of the discovery of faster modern " azoic " colours and other developed reds. Green's new dyeing process was as remarkable a piece of pioneering as the discovery of primuline itself (*J. Soc. Chem. Ind.*, 1888, **7**, 179). Many inventors have over the years devoted their minds to the elaboration of direct cotton dyes suitable for diazotisation and development on the fibre, and the range of such dyes is to-day a large one. Invention in the series still goes on because, although every shade is now represented in the range, the production of certain developed shades, *i.e.*, yellows and greens, presents a problem which has a special challenge for the dyestuff chemist.

Besides the red obtained by diazotising and developing with β-naphthol, primuline gives other shades with other coupling components, *e.g.*, a bordeaux with ethyl-β-naphthylamine, a brown with *m*-phenylenediamine, etc. The diazo-compound is light-sensitive and has been employed in photographic reproduction, thus being the forerunner of the modern diazotype process which is now almost universally used for engineers' drawings (*J. Soc. Chem. Ind.*, 1890, **9**, 1001).

The " ingrain " process, as Green called it, of azo formation on the fibre not only had outstanding industrial importance but was a great piece of pioneering. The effect of increasing the molecular complexity of a substantive dyestuff on the fibre is not merely to modify the shade, but to increase the fastness of the dye. To-day this result is achieved in a number of analogous ways, and Green's invention must be regarded as the parent of the great range of " developed " colours, and in part at least, of the modern " azoic " colours. In the latter the process employed by Green is reversed, a coupling component which has a degree of affinity for cellulose, *e.g.*, β-hydroxynaphthoic anilide, being applied first and the diazo component afterwards. The fastness thus obtained is conditioned by the affinity of one of the components, a feature which is shared by the original " ingrain " process of Green, and which distinguishes it from the older " para-red " process of Holliday. This development is mentioned here in order to emphasize the far-reaching effects of Green's early stroke of genius. Green's employers made the fatal mistake of not patenting primuline, and within a very short time it was successfully imitated by the Swiss firm of Geigy and later by every other dyestuff maker in the world.

The discovery of primuline led to many other new dyestuffs. A study of the action of ammonia on the diazo compound led to the discovery of a method of conferring cotton dyeing properties on the lower thiazoles derived from *p*-toluidine. These ideas were not patented or developed by Green's firm and dyestuffs arising from them were later manufactured by several other firms under the names of thiazol yellow, Clayton yellow, etc. A similar fate befell the valuable basic dyes discovered by Green when the bases obtained by the reaction of sulphur on *p*-toluidine are fully alkylated. A simultaneous discovery by the firm of Cassella led to the introduction of thioflavin T. Green's employers never took up the manufacture of this valuable dyestuff (*J. Soc. Dyers and Col.*, 1917, **33**, 139, 140). The discovery of primuline and its development created a whole chapter of dyestuff chemistry, competent exploitation of which could, in the judgment of well-placed observers in the German industry, have put the English firm in the front rank of the world's chemical manufacturers (*J. Soc. Dyers and Col.*, 1930, **46**, 341).

From now on, until he left industry in disgust, Green was occupied in a series of useful dyestuff inventions and their industrial development. Azo dyes and derivatives of dehydrothiotoluidine occupied most of his attention. This very substantial contribution to industry is, as usual, only sketchily described in the patents and occasional papers appearing in Green's name about this time. Some time after he became chief chemist and manager to the Clayton Aniline Company he took up the study of the stilbene dyes which was to occupy his interest, on and off, for a number of years. This class of dyestuffs is derived from *p*-nitrotoluene-*o*-sulphonic acid by treating it with alkali under various conditions. The first of the dyes which had been obtained by this reaction, known as sun yellow, or direct yellow A, was thought (Bender and Schultz) to be azoxystilbene-disulphonic acid :

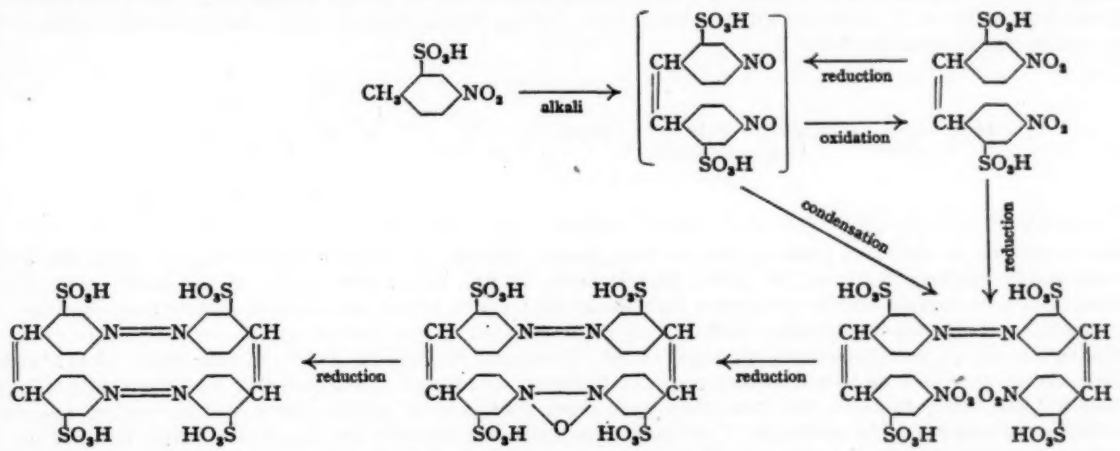


This formula implies reducing conditions in the condensation. On further reduction a redder shade was obtained in which the azoxy group was supposed to be replaced by an azo group (Mikado orange), whereas under

mildly oxidising conditions a greener shade of yellow was obtained (Mikado golden yellow). Green studying these obscure reactions discovered dinitrostilbenedisulphonic acid :

$$\begin{matrix} CH\cdot C_6H_3(SO_3H)\cdot NO_2 \\ \| \\ CH\cdot C_6H_3(SO_3H)\cdot NO_2 \end{matrix}$$

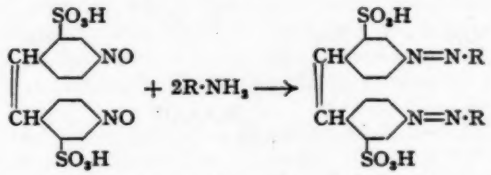
to be the end product of oxidative condensation and from this starting-point he rationalised the preparation of the stilbene dyes. He manufactured them all from one starting-point, dinitrostilbenedisulphonic acid, by alkaline condensation under increasingly strong reducing conditions. In this way he obtained a series of dyestuffs, starting from a greenish yellow and gradually reddening to an orange, which issued under the trade name of stilbene yellows and oranges of various brands. This systematic procedure gave dyestuffs of improved brightness and purity and resulted in valuable business. The stilbenes, together with the thiazoles, still constitute the main bulk of the yellow direct cotton dyes. Remembering that Green had developed the thiazole series also at Clayton, it is not surprising that his company held an important position in this section of the dyestuffs field, a fact recognised jocularly at the time by references to Clayton's " Gelbsucht " (jaundice).



Green's interest in the stilbene class of dyes did not cease with the elaboration of manufacturing methods. He was not satisfied with earlier views on their constitution and began to work on the problem. This work was not completed, however, until ten years later, and is described as a series of papers * published from the Clothworkers' Research Laboratory at Leeds, in which it was finally established that the dyes obtained from *p*-nitrotoluenesulphonic acid were azo compounds, the azo group joining two stilbene residues in their *pp* positions; the *p'p'* positions being occupied by an azo, an azoxy, or nitro groups, according to the degree of oxidation or reduction which had taken place during the alkaline condensation. The mechanism is shown on the scheme above, which postulates the transition formation of a nitrosostilbene, this being the cause of the intense red to blue colouration observed initially when *p*-nitrotoluene derivatives are acted upon by alkali.

Further action of reducing agents results in the formation, first, of a leuco (hydrazo) compound, and, finally, of diaminostilbenedisulphonic acid. The above scheme over-simplifies the actual commercial processes, of course, since a mixture of products is usually obtained consisting not only of stilbene dyes containing a varying ratio of azo, azoxy and nitro groups, but also dinitrodibenzyl derivatives (generally tending to be formed under conditions of milder alkalinity) and traces of azomethine derivatives and aldehydes.

By his work on the constitution and mechanism of the formation of the stilbene dyes, Green paved the way to a further extension of the series. He knew already in his Clayton days that dinitrostilbenedisulphonic acid could be condensed in alkaline solution with various amines to produce stilbeneazo dyes, the formation of which he later attributed to the reactive intermediate nitroso compounds, *e.g.* :



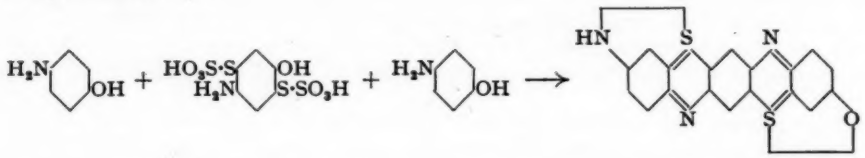
In all probability the products are mixtures, as in the case of the stilbene yellows.

* Green (*J.*, 1904, **85**, 1424); Green, Marsden, and Scholefield (*J.*, 1904, **85**, 1433); Green and Crosland (*J.*, 1906 **89**, 1602); Green, Davis and Horsfall (*J.*, 1907, **91**, 2076); Green and Baddiley (*J.*, 1908, **93**, 1721).

The reaction was later extended by dyestuff manufacturers in several countries to include a wide variety of aminoazo compounds as reactive amines. This has resulted in a considerable number of valuable dyestuffs, chiefly browns, which constitute a major slice of that section of the direct cotton colour range.

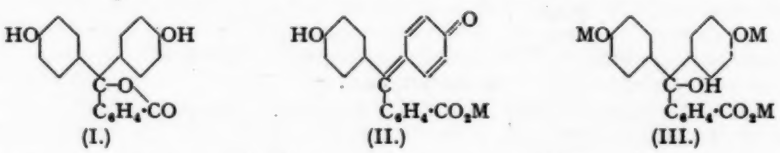
Although developments in the thiazole and stilbene group of dyestuffs represent Green's main achievement in his Clayton period, he introduced a number of miscellaneous azo dyes, chiefly of the direct cotton series, *e.g.*, various rosophenine brands. There is, however, one other main topic to which he gave much attention, though without achieving the degree of success which attended his efforts in other fields.

The sulphide dyes which had already attained some importance, during the last years of Green's stay at Clayton, reached the climax of their development with the arrival of the most important of them all, the famous black obtained by the thionation of 2 : 4-dinitrophenol. The chemistry of the sulphide dyes was unknown and their manufacture was (and still is) based on pure empiricism. Green thought that greater progress could be made if the constitution of the sulphide dyes could be ascertained and their synthesis thereby systematised. He attacked this formidable task, starting from Vidal's view that the sulphide blacks are polythiazines. He attempted a synthesis by making a dithiosulphonic acid of a *p*-phenylenediamine or of a *p*-aminophenol and oxidizing these together with amines, a scheme illustrated by the following example, in which the dithiosulphonic acid obtained by reacting nitrosophenol with sodium thiosulphate in acid solution is reacted first with two molecules of *p*-aminophenol :



This compound in the third phase of the reaction gave a sulphide dye (Green and Perkin, *J.*, 1903, **83**, 1201; Green and Meyenberg, B.PP. 21,832, 1898; 22,460, 1898; 22,847, 1898; 5039, 1899; 18,658, 1899; 4792, 1900). Along such lines several brands of Clayton fast blacks were made, which, on account of their freedom from the by-products of the usual sulphide " melt," were recommended as non-tendering and capable of use in calico printing (Green, *J. Soc. Dyers and Col.*, 1901, **17**, 89; Green and Meyenberg, B.PP. 15,413, 1900; 15,414, 1900). These blacks were lacking in some other respects, however, and Green concluded, too, that the thiazine hypothesis did not apply to them, but that they were more analogous to aniline black in constitution, *i.e.*, were probably polyazines. The molecule is certainly complex, and depends for its dyeing properties not on its nuclear structure, but on the presence of $-S-S-$ groups which, in the sulphide dye-bath, are reduced to $-SH$ groups, which confer solubility. The soluble leuco compound is absorbed by cellulose fibres, on which it reoxidizes to the insoluble $-S-S-$ form and is then resistant to weak alkalis, acids, and to washing. No substantial advance has been made on these views of the chemistry of the sulphide blacks.

The only aspect of theoretical chemistry which interested Green to any extent was the quinonoid hypothesis as a convenient logical means of explaining the tinctorial properties and the chemical behaviour of dyestuffs, as well as many of the steps in their synthesis. He had been immensely attracted by Thiele's explanation of quinonoid addition and his theory of unsaturation and conjugation. Green became a great advocate of these ideas in their application to dyestuffs, and they made his teaching lucid in a high degree (for an example of this see his paper on " Quinonoid addition as the mechanism of dyestuff formation," to the Eighth International Conference of Applied Chemistry). Various studies bearing on this topic are reported in several of his papers * extending over many years. His most challenging contribution was an attack on the textbook explanation † of the well known behaviour of phenolphthalein with alkalis (with A. G. Perkin, *J.*, 1904, **85**, 398). The physical chemists were inclined to the view, first advanced by Ostwald, that colour was the result of ionization, *i.e.*, the colourless acid of phenolphthalein forms salts, the ions of which are coloured. Green made the elucidation of the behaviour of the phthaleins a test case and the evidence of his experiments was accepted by Hantzsch as absolutely disproving the physical theory. Green's contention may be summarized thus : in phenolphthalein the coloured form has the quinonoid configuration (II), the original colourless acid and the colourless salt resulting from the action of excess alkali being represented by (I) and (III) respectively :



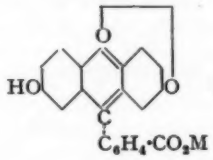
(I.) (II.) (III.)

This view of the *p*-quinonoid structure of phenolphthalein (coloured form) follows, of course, the ideas put

* *Proc.*, 1892, 195; *Proc.*, 1896, 226; *Ber.*, 1899, **32**, 3155; *Z. Farb. u. Textilchem.*, 1902, **1**, 413 ; (with F. M. Rowe) *J.*, 1913, **103**, 508.

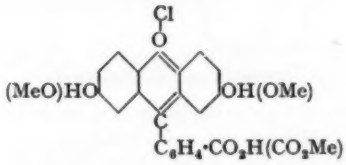
† Ostwald, " Wissenschaftliche Grundlagen der Analytische Chemie."

forward to explain the structure of the triphenylmethane dyes by E. and O. Fischer and by Nietzki, *i.e.*, that they are *p*-quinonoid. In the case of quinolphthalein, for which a *p*-quinonoid formula cannot be written, Green postulated an *o*-quinonoid, oxonium, structure, *i.e.* :

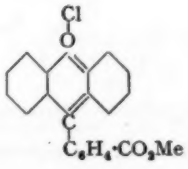


(coloured form)

These views found confirmation in the preparation and study of the ethers and esters of the phthaleins, and in the case of the quinolphthalein the oxonium idea found striking support in the discovery of the series of coloured chlorides (Green and King, *Ber.*, 1906, **39**, 2365; 1907, **40**, 3724. See also *J. Soc. Chem. Ind.*, 1908, **27**, 4; 1909, **28**, 638) :



Analogous oxonium chlorides (Green and King, *Ber.*, 1908, **41**, 3434) of the methyl esters of fluoran were also prepared in order to strengthen the case still further, *e.g.* :



Green made important contributions on the subject of aniline black, on both the chemical and technological sides. Although one of the oldest of dyestuffs, having been observed by Runge in 1834, and having been in industrial use since 1862, its constitution and the mechanism of its formation were unknown. There had, moreover, been no substantial change in the commercial production of aniline black, which takes place on the fibre through the oxidation of aniline hydrochloride, generally with sodium chlorate and a copper salt in the presence of heat and moisture (" ageing "), finishing off with a sodium dichromate bath. Variations of the process consist in the replacement of the copper salt by a ferrocyanide or by a vanadium salt. All these methods require great care to avoid damage to the cotton fibre, which could arise from the presence of hydrochloric acid or oxides of chlorine which could be formed under the conditions of the process. Green endeavoured to mitigate these defects by replacing chlorate oxidation by air oxidation, using a small quantity of *p*-phenylenediamine in the presence of a copper salt as the oxygen carrying system. This process was patented (B.PP. 16,189, 1907; 19,129, 1912) and was successfully reduced to practice by Green and P. F. Crosland in several well-known Continental dye works.

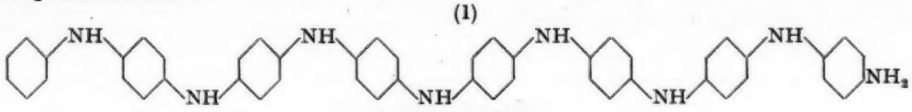
Green speculated, of course, on the rôle of the *p*-phenylenediamine in the new process (*J. Soc. Dyers and Col.*, 1909, **25**, 188) and was led to study the mechanism of the formation of aniline black. He differentiated between " ungreenable " aniline black, which is the end stage of the dyeing process, and products then undergoing investigation at the hands of Willstätter and his school which these workers thought to be aniline black (*Ber.*, 1909, **42**, 2147, 4118; 1910, **43**, 2976; 1911, **44**, 2162), but which in Green's view, merely represented intermediate stages to the formation of the true black. This led to controversy (Green and Woodhead, *J.*, 1910, **97**, 2388; 1912, **101**, 1117; *Ber.*, 1912, **45**, 1955; Green and Wolff, *Proc.*, 1912, **28**, 250; *Ber.*, 1911, **44**, 2570; 1913, **46**, 33; Green and Johnson, *Proc.*, 1913, **29**, 276; *Ber.*, 1912, **45**, 33; 1913, **46**, 3769), but eventually the work of Green's school substantiated his views by identifying the products of the stepwise, *in vitro*, oxidation of aniline with the successive stages in the production of the commercial black and thus establishing a plausible rationale of the process.

According to Green the first stage of the formation of aniline black consists in a series of oxidative additions of aniline to aniline in the manner of indamine formation (*i.e.*, linear) until eight aniline residues have been condensed.

Under carefully controlled conditions in the laboratory the products obtained from the oxidation of aniline salt by any of the commercial aniline black oxidation methods is either emeraldine or nigraniline, which substances are identical with the products well known to the aniline black dyer under these names. Emeraldine and nigraniline are merely oxidation stages of the same leuco compound which is the parent of all these substances,

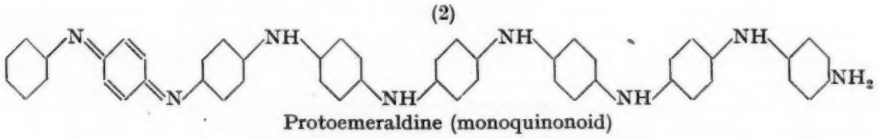
and also of two other oxidation stages which were discovered and named protoemeraldine and pernigraniline. The series is represented thus :

(1)



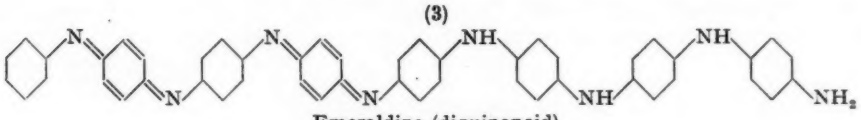
Leucoemeraldine

(2)



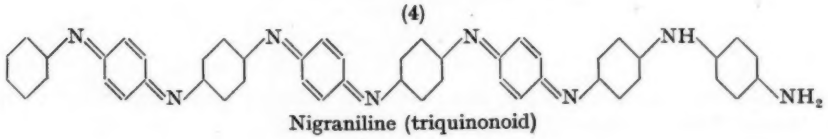
Protoemeraldine (monoquinonoid)

(3)



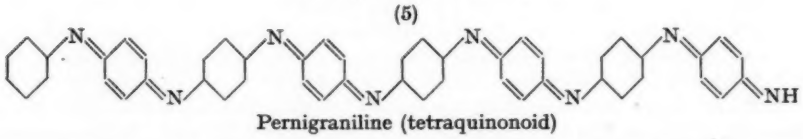
Emeraldine (diquinonoid)

(4)



Nigraniline (triquinonoid)

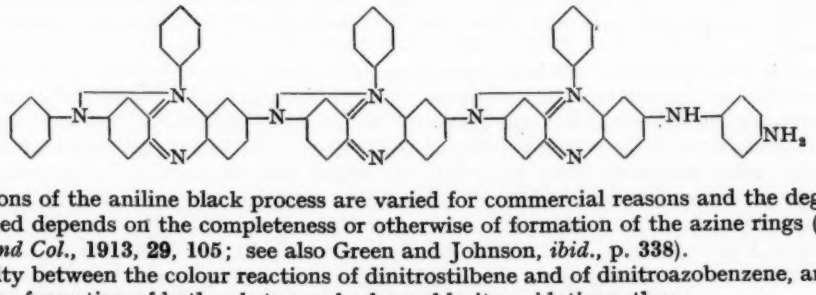
(5)



Pernigraniline (tetraquinonoid)

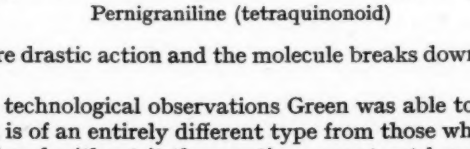
Degradation results from more drastic action and the molecule breaks down to quinone as would be expected from its linear structure.

From his chemical work and technological observations Green was able to demonstrate that the final stage in the formation of aniline black is of an entirely different type from those which precede it, which are pictured above. Free aniline is involved and without it the reaction cannot get beyond the nigraniline stage, *i.e.*, the ungreenable black cannot be formed. Neutral conditions are also necessary, such as in fact prevail in the last stage of the commercial process, the bichromate treatment. In the laboratory such conditions give a product identical with the true aniline black and Green explained the formation of the latter in practice as being due to residual free aniline, still present on the cloth when it emerges from the ager and before it enters the dichromate bath. From these observations Green felt justified in concluding that the last phase in the aniline black process is an oxidative addition of further aniline with ring closure of the safranine type to give a salt (usually the chromate) of the triphenylazoniumoctaphenazine :



The conditions of the aniline black process are varied for commercial reasons and the degree of " ungreenability " attained depends on the completeness or otherwise of formation of the azine rings (Green and Wolff, *J. Soc. Dyers and Col.*, 1913, **29**, 105; see also Green and Johnson, *ibid.*, p. 338).

The similarity between the colour reactions of dinitrostilbene and of dinitroazobenzene, and the parallelism suggested by the formation of both substances by hypochlorite oxidations, thus :



led Green to study the alkaline condensation of nitro-hydrazo compounds (Green and Bearder, *J.*, 1911, **99**, 1960; Green and Rowe, *J.*, 1912, **101**, 2003, 2443), with the object of finding further support for his views on

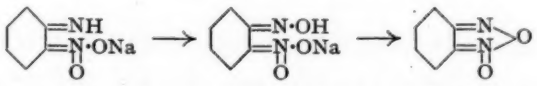
the mechanism of the formation of stilbene dyes. Just as the unstable intermediate products (4 : 4′-dinitrosostilbenes) in the formation of stilbene dyes show a deep bluish-red to blue colour in alkaline solution, so also does the partial reduction product of 4 : 4′-dinitroazobenzene. In both cases the alkaline solutions are readily decolourised by air oxidation, the former yielding dinitrostilbene, the latter dinitroazobenzene. Green's work confirmed the product obtained by reducing 4 : 4′-dinitroazobenzene with ammonium sulphide to be dinitrohydrazobenzene. This dissolves in strong alkali with an intense blue colour and in weak alkali with a violet blue colour. By acidifying the latter solution a compound was precipitated which, from analysis, appeared to be 4-nitro-4′-nitrosohydrazobenzene, $O_2N{\cdot}C_6H_4{\cdot}NH{\cdot}NH{\cdot}C_6H_4{\cdot}NO$, the coloured salts of which would have the quinonoid structure, $MO{\cdot}ON{:}C_6H_4{:}N{\cdot}N{:}C_6H_4{:}NOH$. While, therefore, the resemblance between the intermediate stages in the action of alkali on dinitrostilbene and on dinitroazobenzene is not complete, there is a striking analogy in the final product in the case of the dinitroazo compound, which yields bisnitrobenzeneazoazobenzene (dinitrotrisazobenzene) :

$$\begin{matrix} N{\cdot}C_6H_4{\cdot}N{=}{=}{=}{=}N{\cdot}C_6H_4{\cdot}N \\ \| \qquad\qquad\qquad\qquad \| \\ N{\cdot}C_6H_4{\cdot}NO_2 \quad O_2N{\cdot}C_6H_4{\cdot}N \end{matrix} \text{ cf. Stilbene yellow, } \begin{matrix} CH{\cdot}C_6H_3(SO_3H){\cdot}N{=}{=}{=}{=}N{\cdot}(HO_3S)C_6H_3{\cdot}CH \\ \| \qquad\qquad\qquad\qquad \| \\ CH{\cdot}C_6H_3(SO_3H){\cdot}NO_2 \quad O_2N{\cdot}(HO_3S)C_6H_3{\cdot}CH \end{matrix}$$

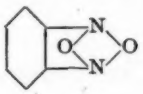
On alkaline reduction tetrakisazobenzene was obtained,

$$\begin{matrix} N{\cdot}C_6H_4{\cdot}N{=}N{\cdot}C_6H_4{\cdot}N \\ \| \qquad\qquad\quad \| \\ N{\cdot}C_6H_4{\cdot}N{=}N{\cdot}C_6H_4{\cdot}N \end{matrix} \text{ cf. Mikado orange, } \begin{matrix} CH{\cdot}C_6H_3(SO_3H){\cdot}N{=}N{\cdot}(HO_3S)C_6H_3{\cdot}CH \\ \| \qquad\qquad\quad \| \\ CH{\cdot}C_6H_3(SO_3H){\cdot}N{=}N{\cdot}(HO_3S)C_6H_3{\cdot}CH \end{matrix}$$

As the result of observations made during the course of the above work Green was led to investigate the oxidation products of *o*-nitroamines, the result of which are reported in a series of papers in collaboration with F. M. Rowe (Green and Rowe, *J.*, 1912, **101**, 2452; 1913, **103**, 508, 897; 1917, **111**, 613; 1918, **113**, 67, 2023; Green, B.P. 25,205, 1912). The behaviour of the nitroanilines with alkaline hypochlorite led Green to postulate the existence of quinonoid salts, of the nitronic acid type, *e.g.*, $C_6H_4{\leqslant}^{NH}_{NO_2Na}$, the reaction proceeding thus in the case of *o*-nitroaniline :



The resulting benz*iso*oxadiazole oxide (or benzfuroxan) was identical with the " dinitrosobenzene " of earlier literature. The constitution finally attributed was the symmetrical one :



because identical products were obtained from the pair of nitrotoluidines: $NH_2 : NO_2 : CH_3 = 1 : 2 : 5$ and $1 : 2 : 4$, and because of other supporting evidence.

Green's last published work in the dyestuffs field related to the so-called " sulphato dyes " and the " ionamines." The major bulk of textile dyeing is carried out in aqueous solution by means of dyestuffs which owe their solubility to the sulphonic acid group attached to an aromatic nucleus. (The sulphonation of rosaniline blue in 1862 by Nicholson was a crucial event in dyestuff history.) Green conceived the idea of solubilisation by means of an extra-nuclear sulphuric ester group and, in collaboration with Saunders, Adams, and Bate, made a series of new dyestuffs of the type $R{\cdot}NH{\cdot}CH_2{\cdot}CH_2{\cdot}O{\cdot}SO_3H$ (R represents the rest of the chromophoric nucleus) which are conveniently and economically prepared by introducing the β-hydroxyethyl group into the dyestuff molecule (generally by reaction between an amino group and ethylene chlorohydrin), and then converting it to the sulphato compound by means of sulphuric acid (B.PP. 181,750, 182,031, 185,612, 186,878; Saunders, *J.*, 1922, **121**, 2667; Green and Saunders, *J. Soc. Dyers and Col.*, 1923, **39**, 39). This invention put a useful new weapon into the hands of the dyestuff chemist.

The sulphonic acid group, which plays such a useful rôle in conferring solubility on dyestuffs, has the drawback of enabling the dyeing process to be reversed under certain conditions, *e.g.*, washing with soap or alkali. A further complication arises from the behaviour of the rayon made from acetylcellulose, which has no affinity for dyes containing the SO_3H group, and thus presented a formidable problem to the dyer when it first appeared on the market. Green overcame these difficulties by attaching to a dyestuff devoid of solubilising groups a methyl-ω-sulphonic acid group, a process easily brought about by condensing formaldehyde-bisulphite with an amino group attached to the dyestuff nucleus. Dyes of this type, *i.e.*, $R{\cdot}NH{\cdot}CH_2{\cdot}SO_3H$, are easily soluble in water in the form of their salts, but, on penetrating the fibre, dissociate with loss of formaldehyde and bisulphite, the residual dyestuff, now no longer soluble in water, being left firmly attached to the fibre. When the dyestuff residue indicated by R in the above formula is suitably chosen, useful products for the dyeing of cellulose acetate rayon are obtained which appeared on the market under the name of " ionamines " (Green and Saunders, B.PP. 197,809, 200,873; Green, Saunders, and Frank, B.PP. 212,029, 212,030; Green and Saunders, *J. Soc. Dyers and Col.*, 1924, **40**, 138).

The above account of Green's experimental work covers the main topics which engaged his attention. Isolated researches * and the numerous lectures which he gave cannot be dealt with here, but the service he rendered to the dye technologist by his work on the identification of dyestuffs in substance and on the fibre should be recorded (Green, *J. Soc. Chem. Ind.*, 1893, **12**, 3; Green, Yeoman, and Jones, *J. Soc. Dyers and Col.*, 1905, **21**, 236; Green and Stephens, *ibid.*, 1907, **23**, 118; Green, Yeoman, Jones, Stephens, and Haley, *ibid.*, p. 252; Green and Frank, *ibid.*, 1910, **27**, 83). This work, extending over a number of years, was eventually published in book form. In spite of the volume of his writing on scientific, technological and economic matters, Green was only responsible for one other book, the *Systematic Survey of the Organic Colouring Matters*, adapted from Schultz and Julius's *Farbstofftabellen*, and incorporating a useful synopsis of information on the principal intermediates (published 1894).

The words of Thomas Browne, quoted at the beginning of this notice, are particularly appropriate to our subject. Green's " pure flame " was his creative genius; his " invisible fire " was his extraordinary faith in the urgency of his cause. They sustained a comparatively frail body through a long life, full to the last of fruitful activity. He saw his cause triumphant in the end, though it required the ordeal of war to bring it home reluctantly to his countrymen.

J. Baddiley.

* Examples are found in the following references: *Ber.*, 1893, **26**, 2772; (with A. G. Perkin) *J.*, 1906, **89**, 1811; (with R. N. Sen) *J.*, 1910, **97**, 2242; *J.*, 1912, **101**, 1113; (with K. H. Vakil) *J.*, 1918, **113**, 35; (with F. M. Rowe) *J.*, 1918, **113**, 955.

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